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D-dimer as a Predictor of Altered Coagulation in HIV Patients in Nigeria

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Summary: Recent medical advances have improved the quality of life and correspondingly reduced the morbidity and mortality associated with HIV infection. However increased life expectancy has led to a relative rise in comorbidities and complications such as alterations in coagulation systems. This study is aimed at the evaluation of D-dimer level as a predictor of thromboembolic risk in HIV patients. A total of 152 HIV positive and negative subjects and control respectively attending the PEPFAR clinic UCH in Ibadan were recruited both for a questionnaire-based survey and a coagulation profile screening. Activated Partial Thromboplastin Time (APTT), Prothrombin Time (PT), D-dimer level the viral load indices of the HIV patients and their CD4 counts were also evaluated. In the subjects, the D-dimer level was significantly higher (193.6 ± 177.00ng/ml) than the controls (118.10 ± 140.58ng/ml) while a significantly lower APTT was also reported (36.22 ± 4.05 seconds) compared to the controls (41.14 ± 8.87 seconds). An evaluation of the coagulation profile in the Highly Active Antiretroviral Therapy (HAART) naive and experienced group revealed only a significant difference (417.4 ± 162.0 versus 268.2 ± 193.5; p value 0.000) in the CD4 counts whilst no significant changes in the coagulation profile. In our study, a higher predisposition to a hypercoagulable state presenting as a short APTT was observed. This finding along with the higher D-dimer level underscores the relevance of the evaluation of this biomarker as an important predictor of thromboembolic event risk.

Keywords*:* HIV, thrombotic event, D-dimer, altered coagulation profile, CD4 count, APTT, PT

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INTRODUCTION

The impact of recent medical advances in HIV patients' health care, early screening and improved health promotion has resulted in a higher survival rate and chronicity of HIV and AIDS infection which has heralded the emergence of previously unknown complications (Antiretroviral Therapy Cohort Collaboration, 2017; Katz and Maughan-Brown, 2017). A notable example of this complication associated with the emergence of the era of Highly Active Antiretroviral Therapy (HAART) is a corresponding increase in reports of thrombotic events in HIV infected patients, a phenomenon previously uncommon among such patients (Copur *et al.*, 2002; Jacobson, Dezube and Aboulafia, 2004). A recent study has also suggested a ten-fold higher prevalence of thrombotic events in this group than in the general population while autopsy studies have revealed significantly higher rates of undiagnosed thromboembolism among AIDS patients (Jacobson, Dezube and Aboulafia, 2004; Freiberg *et al.*, 2016). In most of the patients in these case reports, there were no obvious predisposing risk factors such as surgery, trauma, stasis, nephrotic syndrome, pregnancy or other medical conditions commonly associated with thrombus formation (Heit, 2010).

A possible explanation for this high thrombotic event prevalence has been adduced to the reports of a preferential predisposition of HIV and AIDS patient to a hypercoagulable state. This has been associated with the detection and presence of various abnormalities of clotting related factors such as antiphospholipid antibodies, lupus anticoagulants, protein S & C deficiencies, heparin cofactor II, antithrombin III and elevated von-Willebrand by various authors (Saif, 2000; Jacobson, Dezube and Aboulafia, 2004; Borges *et al.*, 2014).

HIV infection has also been associated with the comorbidities of other medical conditions (such as malignancy, inflammatory and autoimmune disorders) which also increase patients' predisposition to thrombosis. An interesting perspective from recent medical literatures has been the report of deep venous thrombosis, portal vein thrombosis and pulmonary embolism among previously healthy HIV infected

patients recently started on antiviral drugs such as protease inhibitor therapy (Saif, 2000).

The recent growing chronicity of HIV and AIDS infection with resultant chronic inflammation directly and indirectly associated with comorbidities along with the activated coagulation events (both HIV infection features) have been associated with thrombotic events and mortality risks (Neuhaus *et al.*, 2010; Borges *et al.*, 2014). The combined impact of these two features (chronic inflammation and activated coagulation) has thus over the years led to a more extensive mortality predicting biomarkers studies (such as the Strategies for Management of Antiretroviral Therapy (SMART) study). D-dimer was found to be the most predictive biomarker (El-Sadr *et al.*, 2006; Borges *et al.*, 2014).

D-dimer is a specific degradation product of the fibrinolysis of cross-linked fibrin, hence recurrent coagulation and fibrinolysis cycle characteristic of thrombosis and thromboembolic disorders is associated with elevated D-dimer levels. D-dimer therefore serves as an important sensitive biomarker of endogenous fibrinolysis and a detection of an elevated level could be associated with thromboembolic disorder in patients (Funderburg *et al.*, 2010; Heit, 2010; Riley *et al.*, 2016). Aside the role in hypercoagulable state, D-dimer is also an important biomarker of inflammatory changes thus broadening the relevance as an important biomarker of AIDS and non-AIDS events associated with thrombotic events and mortality in HIV and AIDS patients (Freiberg *et al.*, 2016). Various studies on the significant role of D-dimer in the overall pathophysiology of HIV and AIDS morbidity and mortality has also revealed the correlation of d-dimer with endothelial dysfunction, microbial translocation and HIV viral load (Baker, Quick and Russ, 2010; Funderburg *et al.*, 2010).

This study is therefore aimed at the determination of the D-dimer level in adult HIV patients (treatment naïve or on antiretroviral therapy) as a predictor of thromboembolic disease risk and development. The research finding will be significant as the basis for the exclusion of patients not at risk of thromboembolic disorder and for whom urgent additional investigations for DVT or other thromboembolic disorders would be unnecessary.

MATERIALS AND METHODS

This was a case-control, questionnaire driven, interviewer administered, cross-sectional study, where one hundred and fifty-two (152) subjects both HIV and apparently healthy patients were recruited. Ninety-six were all HIV patients attending the PEPFAR Clinic in UCH Ibadan from whom blood samples were taken after responding to the consent form/ questionnaire. The control group comprised fifty-six (56) apparently healthy blood donor individuals who met the study inclusion criteria, gave consent, and tested negative for HIV. Patients with HIV who responded to the questionnaire and consented in writing were also included in the study 1as the cases. Patients on therapeutic dose of anticoagulation within 48 hours prior to sampling, pregnant women, those on hormonal contraceptive, cigarette smokers and non-consenting subjects were excluded.

Data and Sample Collection

The items on the interviewer administered questionnaire included respondents' socio-demographic data, HIV and drug history. Venous blood sample (4.5mls) was collected for D-dimer assay, PT and APTT into 0.5ml of 0.1 molar trisodium citrate, at a ratio of 9:1.

The blood sample was centrifuged at 2000g for 15 minutes to ensure a platelet poor plasma (PPP). PT and aPTT were performed on the freshly prepared citrated PPP according to Essien (1978) & Matchet and Ingrams' (1965) method. The remaining PPP sample was rapidly stored for 4 weeks at -20^{o}C in a single freeze-store cycle for pooled D-Dimer assay thus affording optimal assay response. The D-dimer level was quantified using Biopool TintElize® (Trinity Biotech Plc, Ireland) enzyme-linked immunosorbent assay (ELISA) kit following the manufacturer's instruction. The enzyme immunoassay operates on a double-antibody principle using microtiter plate coated with MA-8D3 monoclonal antibody against D-dimer for the quantitative detection of the D-dimer level.

For the analysis, the D-dimer level for the patients was delineated using the manufacturers normal range (39±12ng/ml) into 3 ranges viz <39, 39 – 130 and >130 ng/ml which was used to categorize the patients based on their D-dimer level as below normal, normal and above normal respectively.

Statistical Analysis

The collected data were entered into Microsoft Excel for collation and proper screening for error. The data were then appropriately coded and statistically analyzed using IBM Statistical Package for Social Sciences (version 24) (IBM Corporation, 2016). Numerical data and continuous variables were summarized descriptively as means and standard deviation while strengths of association were compared using students' t-test. Correlation was determined using Pearsons' correlation coefficient. Categorical variables were expressed as percentages and strength of association was determined using Chi square test. Strength of association and comparison of differences was considered significant at probability level $p < 0.05$.

RESULTS

A total of 152 subjects were recruited into this study comprising of 96 HIV positive subjects (cases) and 56 HIV negative subjects (controls). Among the 96 cases,

33 (34.4%) were males, 63 (65.6%) were females giving a male to female ratio of 1: 1.9 and mean age of 39.02±0.09 years. The cases were consenting attendees of the PEPFAR Clinic University College Hospital (UCH), Ibadan. The controls were made up of 56 apparently healthy and fit blood donors at the UCH. The male to female ratio of the control group was 1.2 :1 while the mean age was 32.2±1.2 years. There was no significant difference in the proportion of the male and female participants, among the cases and controls (p>0.05) but there was a significant difference in the mean ages of the cases and controls. The peak age group was 35 – 45 years with 40 participants (41.7) followed by the 25- 35 group with 35 participants (36.5%).

Majority of the cases were married (68.8%), while 15.6% and 11.5% were singles and widows respectively. Among the controls 48.2% were married while 50% were singles, no widow, widower or separated participants were recruited for the control.

Among the HIV positive and controls, the Yorubas constituted the largest ethnic group 83.3% and 83.9% respectively. There was a significantly lower proportion of cases (2/96; 2.1%) compared to the controls (8/56; 14.3%) with D dimer level below normal level (39–130 ng/ml) (p = 0.001)). Only 46.9% (45/95) of cases but as many as 60.7% of controls (34/56) had D dimer level within normal limits, the difference was significant p = 0.000. The proportion of cases 51% (49/96) who had abnormal D dimer > 130ng/ml was significantly different from 25 % of controls (14) p = 0.001.

As shown in Table 4, an analysis of the quintile distribution of the 45 cases with normal D-dimer level revealed a total of 20 cases in the 3rd to 5th quintile while 20 cases were in the 1st and 2nd quintile. Using an arbitrary high level of 250 ng/ml by the authors, the probability of exceptionally raised D-dimer level > 250ng/ml among HIV patients was significantly higher (OR= 4.6 95%; CI= 1.33- 16.4; p= 0.010) than that of controls.

Table 1: Distribution of Patients and Controls based on the gender and marital status

Demographic Characteristics		Patients	Control	Total
Gender	Female	63/96 (65.6%)	38/56 (67.9%)	101/152 (66.4%)
	Male	33/96 (34.4%)	18/56 (32.1%)	51/152 (33.6%)
Marital Status	Married	66/96 (68.8%)	27/56 (48.2%)	93/152 (61.18%)
	Single	15/96 (15.6%)	28/56 (50%)	43/152 (28.29%)
	Widow	11/96 (11.5%)	-	11/152 (7.24%)
	Widower	1/96 (1.0%)	-	1/152 (0.66%)
	Separated	1/96 (1.0%)	-	1/152 (0.66%)
	Divorced	2/96 (2.1%)	1/56 (1.8%)	3/152 (1.97%)

Table 2: Comparison of Mean D-dimer level, PT and APTT of Patients and Controls

Coagulation Profile	Respondent Category	N	Mean±SD	T-test	P-value	Remark
D-dimer (ng/ml)	Patients	96	193.6±177.00			
	Control	56	118.10±140.58	2.73	0.02	Sig
PT (seconds)	Patients	96	13.46±1.60			
	Control	56	13.29±1.45	0.663	0.66	Not Sig
APTT (seconds)	Patients	96	36.22±4.05			
	Control	56	41.14±8.11	- 4.07	0.000	Sig

Table 3: Cross-tabulation of patients and controls with below normal, normal and above normal D-dimer levels

D-dimer levels		Category of Respondent		Total (n=152)	P-value
Category	(ng/ml)	Patients (n = 96)	Control (n=56)		
Below Normal	<39	2/96 (2.1%)	8/56 (14.3%)	10/152 (6.6%)	0.001
Normal	39 – 130	45/95 (46.9%)	34/56 (60.7%)	79/152 (52%)	
Above Normal	>130	49/96 (51%)	14/56 (25%)	63/152 (41.4%)	

Pearson Chi-Square test value=15.095; degree of freedom = 2

Table 4: Quintile distribution of cases with D-dimer levels within normal range

Quintile	D-dimer (ng/ml)	Cases with normal D-dimer level
1st Quintile	39 – 53.4	20 (44.44%)
2nd Quintile	53.5 – 75	
3rd Quintile	76 – 94.2	25 (55.56%)
4th Quintile	94.3 – 113.2	
5th Quintile	>113.2	

The mean CD4 count of the patients was 296.4 cells/ml (range 11 – 966 cells /ml; median 253 cells/mm^3) while the mean viral load was 9.6×10^5 copies /ml (range = 6×10^1 - 5.9×10^6; median = 1.9×10^3 copies/ml).

There was no significant difference (p = 0.211) between the mean PT of patients on HAART (13.50 seconds) and those not on treatment (13 seconds). The

Table 5: Effect of HAART on cases: D-dimer level, coagulation profile (PT and APTT), and CD4 Count.

Profile	n	HAART Treatment Group	Mean ± SD	Median (Range)	P – value
D – dimer level	84	Treatment	186.8 ± 160.7	135.0 (20.0 – 893.0)	0.85
	12	No Treatment	191.5 ± 202.9	140.0 (40 – 930)	
PT (seconds)	84	Treatment	13.5 ± 1.6	13.0 (10.0 – 21.0)	0.21
	12	No Treatment	13.2 ± 1.7	13.0 (11.0 – 19.0)	
APTT (seconds)	84	Treatment	35.9 ± 3.9	35.0 (23.0 – 50.0)	0.22
	12	No Treatment	37.5 ± 4.1	37.0 (32.0 – 47.0)	
CD4 Counts (cells/mm^3)	84	Treatment	268.2 ± 193.5	238.0 (11.0 – 976.0)	0.00
	12	No Treatment	417.4 ± 162.0	338.0 (115.0 – 614.0)	

Where n is number of patients

Table 7: Comparison of the effect of PI-based HAART and other HAART on patients' coagulation profile and HIV Indices.

Profile	Treatment Groups	n	Mean±SD	P – value
D – dimer level	PI-based HAART	10	173.3 ± 141.1	0.70
	Other HAART	68	195.6 ± 175.4	
PT (seconds)	PI-based HAART	10	13.2 ± 1.5	0.54
	Other HAART	68	13.5 ± 1.6	
APTT (seconds)	PI-based HAART	10	37.4 ± 4.1	0.19
	Other HAART	68	35.6 ± 3.9	
CD4 Counts (cells/mm^3)	PI-based HAART	10	256 ± 151.4	0.78
	Other HAART	68	275 ± 201.4	
Viral Load (10^5 Copies/ml)	PI-based HAART	10	1.02 ± 1.98	0.98
	Other HAART	68	1.06 ± 5.01	

PI = Protease Inhibitors; n = number of cases

Table 8: Correlation of D-dimer level with coagulation profile,
CD4 count and viral load

Variables	Coefficient of correlation (r)	P – value
PT	- 0.011	0.310
APTT	- 0.209	0.010
CD4 Count	- 0.082	0.426
Viral Load	0.011	0.927

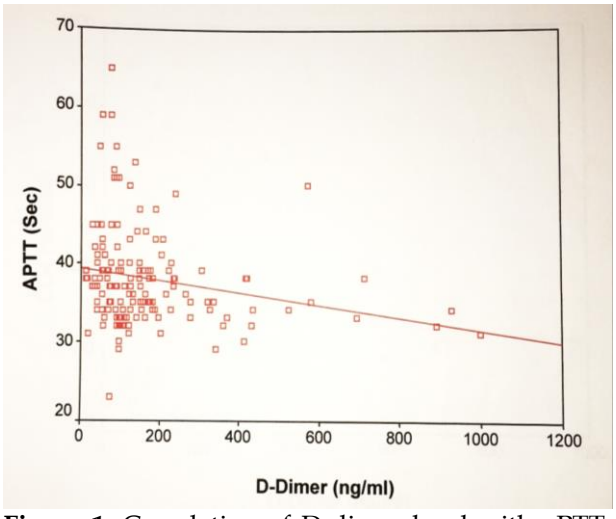

Figure 1: Correlation of D-dimer level with aPTT in HIV patients

difference between the mean aPTT of HAART patient and HAART naïve patients was also insignificant (p = 0.0216). There was no significant difference in the D dimer level of HAART experienced patients and HAART naïve patients; mean 186ng/ml and 191ng/ml respectively p = 0.85 (Table 5).

The HIV cases on HAART were further clustered based on their treatment into those on Protease Inhibitor (PI) based HAART and non-PI treatments. The PI-based treatment group (10/84) were significantly fewer than the non-PI HAART group (68/84). The value for 6 PI based patients were not available. No significant difference was however recorded in the mean level of the coagulation profile (aPTT, PT), D-dimer level, CD 4 count and the patient viral loads.

An evaluation of the relationship between the D-dimer level and the PT of patients revealed an insignificant (p = 0.310) inverse and poor correlation (r = -0.083). As shown in Fig 1., there was a significant weak inverse correlation between the D-dimer level and the APTT level in the patients (r = - 0.209; p = 0.010). The correlation of the D-dimer level with the coagulation profile, CD4 count and viral load are as summarized in Table 8. There was no significant correlation between the D-dimer and viral load of patients (r = 0.011; p = 0.927) while the weak inverse correlation between the D-dimer level and CD4 count (r= - 0.082; p = 0.426) was also not significant.

DISCUSSION

Thrombosis continues to be a progressively emerging complication of HIV and AIDS whose other well-known complications and comorbidities remain challenges to the physicians. The existing confirmatory tests and strategies such as Venography, Duplex ultrasound or Impedance Plethysmography (IPG) are either too expensive, invasive or not readily available during emergencies in some settings. This study was conducted with a view to utilizing D dimer as a screening test. The findings from this study highlights the relevance of D-dimer testing as a potential biomarker of interest in overcoming these shortcomings as the assay can be completed within 10mins with a negative predictive value of as high as 99.6% (Wells et al., 2003). Consequent of this, costs and lives can be saved when early and accurate diagnosis is made.

Our study population had nearly twice as many women as men infected with HIV receiving one form of therapy or the other. A higher prevalence of HIV in women than men has been described by several authors in different places reported a prevalence of 1:1.1 male/female ratio in the general population in Ibadan (Olaleye, 2004) while in Kenya, 23% of women aged 15-19 years were HIV infected compared with 3.5% of men of the same age group (a male to female ratio of 1:6.6) (Nkengasong, 2004). The predominant ethnicity in our study could be ascribed to mirror the tribal mix in the general population of the study.

The higher population of married people in the patient population of our present study is similar to previous reports. This is prime in the attribution of "marriage as a risk factor for HIV infection'' though other reports have reported a higher prevalence of HIV among the young unmarried population due to their predisposition for various risky behaviours (Glynn *et al.*, 2001; Mkandawire-Valhmu *et al.*, 2013; Bekker *et al.*, 2015).

Due to the ensuing improved life expectancy and chronicity of HIV and AIDS and emergence of HAART, there has been increased incidence of altered coagulation in HIV patients. There is a relative dearth of information and available literature on the association of the coagulation profile with HAART regimen.

In our study, APTT in HIV subjects was short but no significant difference was seen in the PT. APTT below the normal implies a hypercoagulable state which predisposes to thrombotic events due to the increased activation of the intrinsic pathways and corresponding reduction in activated protein C effect (Copur *et al.*, 2002; Jacobson, Dezube and Aboulafia, 2004; Tripodi *et al.*, 2004; Zakai *et al.*, 2008). Our finding while not consistent with reports by other authors in which a prolonged PT and APTT were reported among HIV patients (Omoregie *et al.*, 2009; MO and Sylvester N, 2016) underscores the wide variance in the reports of the comparison of coagulation profile in HIV patients and non-HIV patients (Tene *et al.*, 2014; Ephraim *et al.*, 2018).

Furthermore, in our study a significantly higher D-dimer level was reported in the HIV subjects compared to the controls. D-dimer is a specific fibrin degradation product (FDP) formed solely by plasmin degradation of cross-linked fibrin (and not intact fibrinogen). This elevated D-dimer level can be ascribed to an increased reactive fibrinolysis consequent to a hypercoagulable state and thrombotic events. The higher level of D-dimer reported in this study is also consistent with previous reports and further underscores the elevated risks of hypercoagulable state and thrombotic events in HIV patients (Saif, 2000; Jacobson, Dezube and Aboulafia, 2004). The preponderance of hypercoagulable state and other haemostatic disturbances in HIV patients have been associated with abnormalities in various coagulation factors (and the pathways), the potential role of HIV and AIDS comorbidities and the role of antiretroviral drug use (Saif, 2000; Jacobson, Dezube and Aboulafia, 2004; Thulasi Raman *et al.*, 2016). Our study revealed a 4.65 higher risk of an elevated D-dimer level in patients with a likelihood of higher risk of thrombosis. (Cushman, 2007; Tripodi, 2011).

Despite the significance of D-dimer as a predictor of thrombotic event, an elevated value has low specificity for any type of thrombosis as raised level is found in many clinical conditions (including DVT, PE, malignancy, pregnancy, post-surgery, sickle cell crisis and DIC) (Jacobson, Dezube and Aboulafia, 2004; Cushman, 2007; Heit, 2010; Piel, Steinberg and Rees, 2017). It is however a very sensitive marker of increased thrombosis and reactive fibrinolysis which can be used to predict risks of thrombosis (Wells *et al.*, 1995; Cushman, 2007). In addition, D-dimer level can be used as a first line approach in the evaluation of thrombotic risk and to safely identify those with elevated count for further confirmatory tests such as Duplex US or venography. The predictive potential of the D-dimer evaluation (being more convenient, less expensive and much less invasive) would be crucial in reducing the diagnostic time and cost of evaluation of thrombotic complications in HIV patients (both ART naïve and active users) and for further monitoring of those at risk of future thrombotic event.

The D-dimer levels in our treatment experienced and HAART naïve groups despite being lower in them was not significantly different as opposed to the CD4 counts (an important immunological factor in the evaluation and diagnosis of HIV and AIDS and infection severity) which was significantly lower in the treatment experienced group (Thulasi Raman *et al.*, 2016).

There is a wide variance in the relationship between the coagulation profile and HIV status in previous studies. In our study, a significant weak negative correlation was observed between the APTT and D-dimer level while no significant correlation was found between PT, the viral load and CD 4 count. These findings while in contrast with the correlation between PT and D-dimer as previously reported (Omoregie *et al.*, 2009) highlights the significance of APTT and D-dimer as important coagulation profile predictors in HIV patients. A positive D-dimer indicates there is a tendency to significant blood clot formation and its breakdown in the body. It also reflects the presence of abnormally high level of fibrin degradation products e.g. Disseminated Intravascular Coagulation (DIC).

Protease inhibitors (an important class of antiretroviral drugs) have been linked by previous authors with thrombotic complications in HIV and AIDS patients (Henry *et al.*, 1998; Saif, 2000). The mechanism of these thrombotic events while remaining unclear has been proposed to be due to the drug impact on lipid and glucose metabolism. The resultant effect of these metabolic changes have thus been associated with hypercholesterolaemia and endothelial dysfunction which have been suggested as potential contributing factor responsible for the thrombotic complications (Shankar S S and Dube, 2004; Andrade and Cotter, 2006; Thulasi Raman *et al.*, 2016). In our study, the subjects on PI did not appear to be more hypercoagulable judging by their coagulation profile compared to those on other HAART types. In another study, Saif et al 2000,, a mean CD4 count of 166cells/ml was correlated with an increased predictive risk of thrombotic complication due to the severity of the infections in these patients. (Saif, 2000; Saif, Bona and Greenberg, 2001; Jacobson, Dezube and Aboulafia, 2004). The high CD4 count reported in our study compared to this previous study could then be attributed as a potential factor responsible for the absence of a significant hypercoagulable state.

D-dimer is a specific FDP that is formed only by the plasmin degradation of cross-linked fibrin and not by plasmin degradation of intact fibrinogen. D-dimer are unique in that they are the breakdown products of a fibrin mesh that has been stabilized by factor XIII. Thus the presence of D-dimer indicates the fibrin has been formed and degraded (MGH Pathology service, 2006). D-dimer and FDP can be positive with DIC or thrombosis, including DVT, PE and myocardinal infaction. They also may be positive in liver disease due to decreased hepatic clearance. They can also become elevated postoperatively and in eclampsia, sickle cell crises, cancer patients and other conditions which are prethrombotic (MGH Pathology service, 2006). The results of this study highlights the elevated D-dimer level in HIV patients with potential consequences of altered coagulation parameters. We therefore recommend routine screening and monitoring of HIV patients for deranged coagulation profile using the baseline D-dimer values to predict the at-risk subjects with a view to promptly diagnose and treat thrombotic events at the earliest suspicion.

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