Journal of Cancer and Tumor International

9(3): 1-6, 2019; Article no.JCTI.52110
ISSN: 2454-7360

Reduced P53 Protein Level and Evidence of Ongoing Coagulation among HIV-Infected Persons Accessing Treatment at University of Calabar Teaching Hospital, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Author ECA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AOO and JOA managed the analyses of the study. Authors JOA and EEO managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JCTI/2019/v9i330111
Editor(s):
(1) Dr. William CS Cho, Queen Elizabeth Hospital, Hong Kong.
Reviewers:
(1) Karen Cordovil, Brazil.
(2) Ibama, Asiton-a Solomon, Federal University of Technology, Nigeria.
Complete Peer review History: http://www.sdiarticle4.com/review-history/52110

Original Research Article

Received 10 August 2019
Accepted 15 October 2019
Published 26 November 2019

ABSTRACT

Aims: To assess tumour suppressing activity and ongoing coagulation among persons living with HIV infection and accessing care in the University of Calabar Teaching Hospital, Nigeria.
Study Design: Case-control study.
Place and Duration of Study: University of Calabar Teaching Hospital Calabar, Nigeria, between April 2018 and November 2018.
Methods: Ninety persons living with HIV infection who were attending clinics at the University of Calabar Teaching Hospital were enrolled with ninety age and sex-matched HIV seronegative individuals who served as control subjects. The blood specimen was collected from each participant for analyses of CD4 cell and full blood counts by automation, serum was used for the assays of P53 protein and D-dimer levels using enzyme-linked immunosorbent assay test kits. Data analysis was done using SPSS version 22.0. Student t-test was used to compare means between test and

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control subjects. One-way analysis of variance was used to compare means across the HAART-naïve and two other groups on different HAART protocols. Statistical significance was drawn at a p≤ 0.05.

Results: The CD4 cell count and P53 protein level reduced while D-dimer level increased in HIV infection. Platelet count also reduced while platelet distribution width increased with the condition. While CD4 cell count improved with Highly Active Antiretroviral Therapy administration, D-dimer level, mean platelet volume and platelet distribution width reduced.

Conclusion: This study observed reduced tumour suppression and increased coagulation activities alongside immunosuppression in HIV infection.

Keywords: Coagulation; HIV infection; immunosuppression; tumour suppression.

1. INTRODUCTION

The health challenges associated with HIV infection in Africa are often compounded by issues that border on ignorance and poverty. It has been previously observed that in Calabar, screening for HIV infection is mainly occasioned by conventional antenatal care and prospective blood donation [1]. Unfortunately, the conventional antenatal care is yet to be fully accessed with the result that some infected pregnant women are not detected on time and the risk of vertical transmission continues to be a challenge [2]. Thus, late presentation to hospital remains a militating factor to early intervention [3]. Among the infected persons in our local population, widespread derangement in biomarkers and morbidity indicators that mirror poor health status prevail [4]. However, disease progression from HIV infection to acquired immune deficiency syndrome (AIDS) depends on proper management which in turn relies on timely detection of morbidity indicators and subsequent intervention [4,5].

An important aspect of the viral invasion of host immunity in HIV infection is the depletion of the T-helper CD4 cell population. In most resource-poor settings where the viral load cannot be ascertained, CD4 cell count remains the biomarker for severity of the infection and its subsequent progression to AIDS. Its degree of depletion is considered in the assessment of the severity of immunosuppression. While there is much focus on immunosuppression, the attendant morbidities of HIV infection are rarely investigated locally, thus limiting the scope of management and care offered to infected persons. Coagulation disturbances and cancer have been identified as factors for increased mortality among people living with HIV infection. Impaired immunity and the development of these other morbidities are thought to reflect an unending cycle that eventually progresses HIV infection to AIDS [6,7,8,9,10]. In Nigeria, particularly Calabar, not much is known about the nature of the hemostatic disturbance seen in HIV infection. There is also the paucity of information on levels of cancer biomarkers among infected subjects. This study was carried out to assess tumour suppressing activity (using serum p53 protein as a marker) and ongoing coagulation (using d-dimer in addition to platelet parameters) among HIV-infected subjects.

2. MATERIALS AND METHODS

The prevalence of HIV infection in Cross River State, Nigeria was 4.4% as reported by the National Action Committee on AIDS in 2018. Although the sample size derived from the mentioned prevalence is 64.6, it was extended to 90 because the study required comparable numbers from three sub-groups (persons who were newly diagnosed and were yet commence treatment and those who were being treated with either Tenofovir+Lamivudine+Efavirenz (TLE) orLamivudine+Zidovudine+Nevirapine (LZN). The study adopted a mixed sampling method; convenient sampling technique since the enrolled subjects was accessing care at the hospital and a stratified approach to obtain comparable numbers from the sub-groups. Ninety persons living with HIV infection who were attending clinics at the University of Calabar Teaching Hospital were enrolled with ninety age and sex-matched HIV seronegative individuals who served as control subjects. The enrollment of persons living with HIV infection took into consideration certain sub-groups based on the commencement of highly active antiretroviral therapy (HAART). Thirty persons were newly diagnosed and were yet to embark on HAART. The remaining 60 were already undergoing treatment. The blood specimen was collected from each participant for analyses of CD4 cell and full blood counts by automation, serum was used for the assays of P53 protein and D-dimer

levels using enzyme-linked immunosorbent assay test kits. Data analysis was done using SPSS version 22.0. Student t-test was used to compare means between test and control subjects. One-way analysis of variance was used to compare means across the HAART-naïve and two other groups on different HAART protocols. Statistical significance was drawn at a $p \leq 0.05$.

3. RESULTS AND DISCUSSION

3.1 Results

Persons living with HIV infection who participated in this study were adults from eighteen years and above. The age group with the highest number of participants was 36-45 years which featured 34.4% (31 out of 90) of all the persons. This was followed by age group 26-35 years which had 31.1% (28 out of 90) of the subjects. The least number of participants, 7.8% (7out of 90) came from the group above 55years of age. More females 63.3% (57 out of 90) than males 36.7% (33 out of 90) were observed accessing medical care at the study centre. Also, more than half of these persons were married 60% (54 out of 90) at the time of the study. A third of the persons living with HIV infection were enrolled from those newly diagnosed. The remaining 60 were already undergoing treatment. Two HAART protocols were observed among subjects who were being treated; Tenofovir+Lamivudine+Efavirenz (TLE) and Lamivudine+Zidovudine+Nevirapine (LZN). Subjects on TLE were 48.3% (29 out 60), while those on LZN were 51.7% (31 out of 60) (Table 1).

The CD4 cell count and P53 protein level were found to be reduced while the D-dimer level increased in HIV infection. The platelet parameters considered in this study were platelet count, mean platelet volume (MPV) and platelet distribution width (PDW). Platelet count was observed to be reduced while platelet distribution width (PDW) increased with the condition (Table 2).

Subjects on highly active antiretroviral therapy (HAART) were either taking Tenofovir+Lamivudine+Efavirenz (TLE) or Lamivudine+Zidovudine+Nevirapine (LZN). Both drug combinations impacted similarly to the measured parameters. While CD4 cell count improved with HAART administration, D-dimer level, mean platelet volume (MPV) and PDW reduced (Table 3).

3.2 Discussion

Although HIV infection affects all ages, the current study enrolled persons from eighteen years of age and above mainly for the ease of obtaining consent. The age group with the highest number of participants was 36-45 years which featured 34.4% persons. This was followed closely by age group 26-35 years which

Table 1. Demographic parameters of studied subjects

Parameter	HIV-infected persons n=90 (100%)	Control subjects n=90 (100%)
Age (years)		
≤25	10 (11.1)	10 (11.1)
26-35	28 (31.1)	29 (32.2)
36-45	31 (34.4)	31 (34.4)
46-55	14 (15.6)	15 (16.7)
>55	7 (7.8)	5(5.6)
Gender		
Females	57 (63.3)	55 (61.1)
Males	33 (36.7)	35 (38.9)
Marital status		
Single	29 (32.2)	36 (40.0)
Married	54 (60.0)	50 (55.5)
Widowed	7 (7.8)	4 (4.5)
HAART initiation		
Treatment-naïve	30 (33.3)	
Treatment on course	60 (66.7)	
HAART protocol		
TLE	29 (48.3)	
LZN	31 (51.7)	

Table 2. CD4 cell count, P53 level, D-dimer level and platelet parameters of HIV-infected persons and control subjects

Parameter	Control subjects (n=90)	HIV-infected subjects (n=90)	p-value
CD4 (cells/ml)	868.78±221.03	509.29±311.15	0.000
P53 (ng/l)	1816.87±575.33	1587.37±529.01	0.006
D-dimer (pg/ml)	2816.33±696.38	4752.13±515.32	0.000
Platelet count (x 10^9/l)	255.26±64.31	215.99±59.98	0.000
MPV (fl)	9.13±0.86	9.21±0.95	0.550
PDW (%)	14.84±0.35	18.89±9.11	0.000

Table 3. Impact of routine HAART protocols on the measured parameters

Parameter	HAART-naïve n=30	HAART (TLE) n=29	HAART (LZN) n=31	p-value
CD4 (cells/ml)	377.63±191.18*	634.93±368.42	519.16±304.15	0.005
P53 (ng/l)	1653.20±555.32	1682.07±414.78	1435.06±578.43	0.138
D-dimer (pg/ml)	4966.23±518.45*	4695.21±435.10	4598.19±526.79	0.014
Platelet count (x 10^9/l)	217.23±65.93	220.31±57.05	210.74±58.12	0.822
MPV (fl)	9.79±0.99*	8.81±0.81	9.02±0.78	0.000
PDW (%)	26.98±12.36*	14.89±0.56	14.80±0.50	0.000

*Key: * =HAART-naïve significantly different from both HAART (TLE) and HAART (LZN)*

had 31.1% subjects. Altogether, the age group between 26-45 years constituted 65.5%. This frequency pattern for age, combined with that for gender (63.3% female participation), as well as that for marital status (60% of married persons), reveals a significant pattern. It implies that among adults living with HIV infection, women of childbearing age constitute the highest group receiving medical attention to HIV infection. This trend has implications for the control of HIV infection in this locality as the risk of mother to child transmission could be better managed within conventional health facilities.

This study observed alongside a lower value of CD4 cell count, reduced serum p53 protein level. In the progression of HIV infection to AIDS, both declines in immunity and the development of cancer are considered important morbidity and mortality factors [6,8,9,10,11]. In resource-poor settings, cancer screening among HIV-infected persons is yet to commence despite the need to monitor this aspect of health for infected persons [12]. The p53 gene and its protein play a significant role in the immunosuppression of cancer and is also known to mediate against the replication of the human immunodeficiency virus, thus serving as a host-restriction factor. It is therefore thought that the silencing of the p53 pathway promotes both viral replication and disease progression in HIV infection [13,14]. The two HAART protocols in use at the health facility were observed to improve the CD4 cell count but showed no significant variation for the serum p53 protein. There may need to go beyond this stage of treatment if tumour immunosuppression is to be addressed. This could impact on disease progression from HIV infection to AIDS.

In addition to the reduced serum p53 protein, the studied population showed evidence of activated coagulation as observed in the lower platelet count but higher PDW and D-Dimer values. Although the finding of lower platelet count could arise from insufficient production as well as increased consumption, the observation of higher PDW value suggests the later. The PDW represents the variability in platelet size and is thought to be an important marker of platelet activation [7,15,16,17,18,19]. More importantly, D-dimer is the degradation product of fibrinogen and fibrin during fibrinolysis. Although various fibrin-degradation products result from plasmin-mediated breakdown, D-dimers is considered a specific marker for fibrinolysis in that only fragments originating from fibrin polymers that had undergone factor XIII mediated cross-linking retain an intact covalent bond between two adjacent D domains; hence the term D-dimers. It, therefore, reflects ongoing activation of the hemostatic system and more specifically represent breakdown products of cross-linked fibrin clot formation [20,21,22].

4. CONCLUSION

This study concludes that there is reduced tumour suppression and increased coagulation activities alongside immunosuppression in HIV infection. The D-dimer, MPV and PDW mean

values also varied across the HAART groups about the HAART-Naïve group. The drugs impacted positively on the coagulation parameters studied, thus suggesting a better hemostatic state among persons living with HIV infection who are on HAART compared to those yet to commence HAART.

CONSENT AND ETHICAL APPROVAL

Ethical approval was obtained from the University of Calabar Teaching Hospital Health Research Ethics Committee, while written informed consent was obtained from each participant.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/52110