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Research

Abnormal coagulation profile in people living with HIV-AIDS on combined Antiretroviral Therapy: findings from a case-control study in the Ho municipality, Ghana

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Abstract

Introduction: Although combined Anti-Retroviral Therapy (cART) has improved the quality of life and survival in people living with HIV-AIDS (PLWHA), there have been reports of increased non-AIDS related co-morbidities such as coagulopathies. The objective of this study was to assess the effect of cART on the coagulation profile of PLWHA. **Methods:** This case-control study recruited 110 PLWHA (65 patients on cART, and 45 cART naïve patients) from the antiretroviral therapy unit of Volta Regional Hospital, Ho. Blood was collected for prothrombin time (PT), activated partial thromboplastin time (APTT)and platelet count. **Results:** cART naïve individuals had a high PT ($p < 0.001$; 17.2 vs 13.8) and APTT ($p = 0.081$; 59.7 vs 55.3) compared to their counterparts on cART. Also, INR was significantly lower in cART-treated PLWHA ($p<0.001$). Platelet count was high in participants on therapy compared to their naïve counterparts (204.7 vs 193.6, $p = 0.402$). Patients on zidovudine + nevirapin + efavirenz therapy had a significantly lower PT compared to those on zidovudine + lamivudine + efavirenz therapy {$p = 0.02$, 13.23 vs 14.66}. Additionally, PLWHA on zidovudine + nevirapin + efavirenz had reduced APTT compared to those on zidovudine + lamivudine + efavirenz therapy, or zidovudine + lamivudine+ nevirapine therapy ($p = 0.058$; 47.55 vs 56.81 vs 56.85 respectively). **Conclusion:** HIV infection adversely affects the coagulation profile in PLWHA which improves with cART. Barring the existence of other comorbidities, cART with zidovudine + nevirapin + efavirenz combination could be the treatment of choice as it significantly improves the coagulation profile in PLWHA.

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Introduction

Human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS), is a global pandemic caused by infection with human immunodeficiency virus [1, 2]. As of 2016, approximately 36.7 million people were living with HIV globally [3]. Ghana's HIV prevalence rate currently stands at 2.4% according to the Ghana Aids Commission [4]. The main immunological complication of HIV infection is cellular CD4+ T-lymphocyte depletion, for which various causal mechanisms have been proposed. Among these are HIV-induced cytolysis; dysregulation of cytokines; cytotoxic T lymphocyte responses and HIV-induced autoimmune reactions [5]. The introduction of combined antiretroviral therapy (cART) for treatment of HIV infection has generally been accepted as the gold standard in the management of HIV patients [6]. Since the advent of effective antiretroviral therapy (ART) for HIV, there has been a substantial decrease in deaths related to HIV/AIDS [7] as well as non-AIDS associated events. Different anti-retroviral agents target different steps in HIV replication including glycoprotein components 120 and 41 as well as enzymes involved in HIV replication [8]. Recently, Omoregie et al., found that HIV patients with CD4 count < 200 cell/μL had higher PT and APTT values; although only PT correlated with CD4 counts [9]. They opined that the progression of the HIV infection consequently causes endothelial dysfunction and liver damage that might result in severe clotting impairment [9]. Another study also found that 34.88% of the sampled HIV infected individuals had deranged partial thromboplastin time activated with kaolin (PTTK), with 9 out of 10 of those with the deranged PTTK also demonstrating thrombotic disorders as a result of the presence of circulating anticoagulant [10]. However, another study by Dikshit et al., found no case of coagulation abnormalities in the HIV patients studied [11] suggesting the need for further studies to clarify the impact of HIV infection as well as cART therapy on the coagulation profile of these patients. In this study we sought to compare the coagulation profiles of HIV persons on cART to that of cART naïve HIV patients to assess the coagulation profiles and how cART therapy might impact these factors.

Methods

Study setting/study design/participants: This hospital-based case-control study was conducted from January to April 2014 at the Volta Regional Hospital in Ho, the capital of the Volta Region of Ghana. Confirmed PLWHA (110), comprising 65 on cART and 45 cART naive patients visiting the ART clinic were recruited onto the study. The antiretroviral drugs being used by the participants were various combinations (CB) of Zidovudine (AZT) + Lamivudine (LAM) + Efavirenz (EFV) as CB1; AZT + LAM + Nevirapine (NEV) as CB2; AZT + NEV + EFV as CB3. However, participants with myeloproliferative disorders, liver diseases, those on other drugs apart from cART and those on anticoagulant therapy where excluded. Other clinical and demographic information was collected using questionnaire. Ethical approval was obtained from the University of Cape Coast Institutional Review Board (UCCIRB) and the Ethical Committee of the hospital before commencement of the study. Written informed consent was sought from the participants before collecting their data and samples.

Blood Sample Collection and processing: Five (5) ml blood was collected from the study participants for coagulation studies (PT, APTT, INR) (citrated tubes at blood to anticoagulant ratio of 9:1) and full blood count (FBC) (EDTA anticoagulated tubes). The blood for coagulation studies was centrifuged at 1500 rpm for 3-5 minutes and the plasma separated.

PT, APTT, FBC estimation: The plasma was used to estimate prothrombin time (PT), activated partial thromboplastin time (APTT) using standard operating procedures as previously described [12] EDTA anti-coagulated blood was used to estimate the WBC, lymphocyte count, platelet count by using the automated Sysmex X-500i haematology analyzer (Sysmex Corporation, Japan). The WBC stratification was based on previously recommended reference range in the literature [13].

Statistical analysis: The data were entered into Microsoft excel and analyzed using IBM Statistical Package for Social Sciences (SPSS) statistics for windows, version 21.0 (Armonk NY; IBM Corporation). Data were expressed as means and percentages for different variables. Comparison between variables was done using Chi-square test. One-way ANOVA was also used to compare means of scores of more than two groups. Continuous variables were analyzed using unpaired student's T -test for variation among HIV naïve individuals and those on cART. Statistical significance level was set at $P<0.05$.

Results

Table 1 summarizes the general characteristics of the study participants. The PT (13.83 ± 2.05 vs 17.24 ± 4.24), and INR (1.2 ± 0.2 vs 1.44 ± 0.4) were significantly reduced in Patients on cART compared to the cART naïve patients ($p<0.001$, both in patients on cART). Though the APTT was also lower in the patients on cART compared to cART naïve patients, this did not reach statistical significance ($p=0.081$). However, although platelet counts were higher in patients on cART compared to cART naïve patients, the difference did not reach statistical significance ($p=0.402$). In addition, WBC counts were reduced in patients on cART compared to cART naïve patients. Table 2 shows the coagulation profile of the study participants. Majority of the participants on cART had a normal PT (10-15 sec) compared to the cART naïve participants (75.4% v 33.3%; $P< 0.001$). Moreover, majority of the cART naïve participants had prolonged PT (> 15 sec) than those on cART (66.7% v 23.1%; $P< 0.001$) suggesting a potential role of cART in restoring the PT. In addition, a higher proportion of cART participants (21.5%) had estimated APTT within the reference range, compared to 13.3% cART naïve participants. Interestingly, whereas 78.5% of cART participants had prolonged APTT (APTT >45 seconds), 86.7% of cART naïve participants had prolonged APTT. The effects of different cART regimen on PT, APTT, platelet and WBC counts were also investigated (Table 3). Participants on drug combination 2 (AZT+LAM+NEV) had a significantly higher mean PT and INR when compared to those on drug combinations 3 (AZT+NEV+EFV) and 1 (AZT+LAM+EFV) respectively ($p=0.020$, one-way ANOVA). Comparatively, CB2 appeared less able to restore PT (40.7% had PT>15 seconds) in contrast to those on CB1 (7.4%) or CB3 (18.2%) therapy ($p=0.013$; one-way ANOVA). With regards to the APTT, participants on CB3 had lower mean APTT compared to CB1 or CB2 {47.55 versus 56.81 (CB1) or 56.85 (CB2); $p=0.058$}. More importantly, a significantly greater proportion of participants on CD3 had APTT in the reference range when compared to CB1 and CB3 (63.6% versus 11.1% & 14.8% respectively; $p <0.001$). Moreover, whereas only 36.4% of participants on CB3 had prolonged APTT (APTT >45 seconds), significantly higher proportions of participants on CB1 (88.9%) and CB2 (85.2%) had prolonged APTT ($p< 0.001$). In addition, whereas a lower proportion of participants on CB3 had $<4x10^3/mm^3$ compared to CB1 and CB2 {27.3% versus 63% (CB1), or 59.3% (CB2); $p = 0.116$}, a higher proportion of participants on CB3 had WBC of 4-10x103/mm^3 when

compared to CB1 or CB2 {72.7% versus 37% (CB1), or 37% (CB2); p = 0.093}.

Discussion

In this study we determined the effect of cART on the coagulation profile of HIV/AIDS patients. Our results showed that participants on cART had lower mean PT and APTT, but higher platelet counts when compared to their cART naïve HIV patients. In addition, whereas the PT and APTT of cART participants were generally within the reference range, these parameters for the cART naïve participants were generally higher than the upper limit of the reference range suggesting a potential role of cART to restore and/or correct these coagulation factor derangements. Recently, Omokaro et al., reported that HIV seropositive patients have higher APTT and PT than HIV seronegative persons [9]. In spite of the increased APTT and PT, they further stated that only PT positively correlated with the CD4 counts in HIV seropositive individuals and suggested endothelial dysfunction as underlying defect in the prolonged APTT and PT in these patients. Although our study did not assess the functional capacity of the liver in these participants, it could be argued that the improved PT and APTT reported herein amongst the participants on cART could have been the consequence of cART improving the hepatic functional ability to synthesize some coagulation factors that are indirectly assessed through the PT and APTT assay.

Interestingly, this study also showed that the type of cART regimen or drug combination has significant effect on the restoration of normal coagulation profile in these patients. Patients on cART combination 3 [Zidovudine (AZT) + Nevirapine (NEV) + Efavirenz (EFV)] appeared to have a more favourable coagulation profile as these participants had lower mean APTT and PT compared to those on cART combination 1 [AZT + Lamivudine (LAM) + EFV] or cART combination 2 [AZT+LAM+ Nevirapine (NEV)]. In addition, a higher proportion of participants on cART combination 3 had their APTT and PT restored to the reference range values when compared to CB1 or CB2. This is an interesting observation considering that it is generally proposed that two nucleoside reverse transcriptase inhibitors should form the backbone of cART therapy [14] for optimal response. cART combination 3 however contained only one nucleoside reverse transcriptase inhibitor (AZT) and two non-nucleoside reverse transcriptase inhibitors (NEV + EFV). This is also against the backdrop of previous report that suggested an association of hepatotoxicity with nevirapine treatment [15]. It will be interesting to investigate the variability in the responses of different races or population groups to the various cART combinations. Moreover, whereas cART naïve HIV/AIDS patients had higher mean total WBC counts compared to cART treated HIV patients, CB3 was more effective in raising the WBC counts when compared to CB1 or CB2. As high as 72.7% of participants on cART CB3 had their WBC counts restored to the reference range when compared to 37% participants on either cART CB1 or CB2. Our findings agree with a previous report by Omoregie et al who showed that HIV-positive patients have significantly lower CD4 and platelet counts than HIV-negative subjects [9]. We propose that the increased WBC counts in participants on cART in this study might be due to a cART being able to restore bone marrow haematopoietic activity [16]. Our study, however, had a few limitations. As malnutrition has been shown to be a major factor in the HIV/AIDS disease burden in worldwide [17], it is reasonable to suppose that the nutritional status of the patients investigated might have had effect on the extent to which cART impacted the coagulation profile of these patients. We did not however, investigate effects of the indigenous dietary inclinations of the participants' vis-à-vis cART combination and coagulation profile. More so, this study did not investigate the duration of cART therapy on the coagulation parameters.

Conclusion

Findings from this study suggest that, these type of cART regimen could affect the coagulation and other haematopoietic profiles in PLWHA. Moreover, Zidovudine + Nevirapine + Efavirenz combined therapy had the most beneficial effects in correcting for PT, APTT and total WBC counts in the population studied. Future studies addressing the associations between local dietary choices, cART combination, and coagulation profiles of PLWHA would likely yield interesting findings.

What is known about this topic

- HIV infection causes coagulation derangement and predisposes to venous and arterial thrombosis.

What this study adds

- cART could improve the coagulation profile in PLWHA;
- Different cART regimens could impact differently the coagulation profiles of PLWHA, with the Zidovudine + Nevirapine + Efavirenz combination being potentially most beneficial;
- Combining one nucleoside reverse transcriptase inhibitor with two non-nucleoside reverse transcriptase inhibitors may offer better chance of restoring deranged coagulation profile in patients on cART.

Competing interests

The authors declare no competing interests.

Authors' contributions

RKDE, PA, JB and JEA conceived of the study and participated in its design and coordination. RKDE, PA and JEA were involved in the recruitment of participants, data collection and analysis. RKDE, PA and OC drafted the manuscript. HA, OC and PA provided analytic and statistical support. All authors read and approved the final manuscript.

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Tables

Table 1: General characteristics of study participants
Table 2: Coagulation profile of study participants
Table 3: Coagulation profile of study participants on cART stratified by the type of cART combination

References

1. Sepkowitz KA. AIDS-The First 20 Years. New England Journal of Medicine. 2001; 344(23): 1764-1772.**PubMed** | **Google Scholar**

2. Chan DC, Kim PS. HIV entry and its inhibition. Cell. 1998; 93(5): 681-4. **PubMed** | **Google Scholar**

3. World Health Organisation. **Global Health Observatory (GHO) data** . 2016. Accessed 6 November 2107

4. Ghana AIDS Commision. **Summary of the 2016 HIV sentinel survey report**. 2016. Accessed 5 November 2017

5. Okolie MN, Eghafona NO, Omoregie R. **Anti-Human Immunodeficiency Virus (HIV) Agents**. 2003. Accessed November 2017

6. Odunukwe N, Idigbe O, Kanki P, Adewole T, Onwujekwe D, Audu R, Onyewuche J. Haematological and biochemical response to treatment of HIV-1 infection with a combination of nevirapine + stavudine + lamivudine in Lagos Nigeria. Turk J haematol. 2005; 22(3): 125-131. **PubMed** | **Google Scholar**

7. Palella FJ, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, Holmberg SD. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr. 2006; 43(1): 27-34. **PubMed** | **Google Scholar**

8. Rathbun RC. HIV consensus guideline recommends antiretroviral treatment regardless of CD4 count, new regimens and possible regimen change for chronic low level viraemia. Evid Based Med. 2013; 18(4): 149-50. **PubMed** | **Google Scholar**

9. Omoregie R, Osakue SI, Ihemeje V, Omokaro EU, Ogeferet HO. Correlation of CD4 count with platelet count, prothrombin time and activated partial thromboplastin time among HIV patients in Benin City, Nigeria. West Indian Med J. 2009; 58(5): 437-40. **PubMed** | **Google Scholar**

10. Kasthuri AS, Sanjeevan S, Kar PK. A study of hematological manifestations of HIV infection. Indian J Sex Transm Dis. 2006; 27(1): 9. **Google Scholar**

11. Dikshit B, Wanchu A, Sachdeva RK, Sharma A, Das R. Profile of hematological abnormalities of Indian HIV infected individuals. BMC Blood Disord. 2009; 9: 5. **PubMed** | **Google Scholar**

12. Dacie JV, Lewis SW. Practical haematology-11th edition. London Churchill Livingstone. 2012. **Google Scholar**

13. Barabara J Bain IB, Michael A Laffan, Mitchell Lewis , Dacie S and Lewis. **Dacie and Lewis Practical Haematology: 11th Edition**. 2011. Accessed 6 November 2017

14. Piacenti FJ. An update and review of antiretroviral therapy. Pharmacotherapy. 2006; 26(8): 1111-33.**PubMed** | **Google Scholar**

15. Haas DW, Bartlett JA, Andersen JW, Sanne I, Wilkinson GR, Hinkle J, Rousseau F, Ingram CD, Shaw A, Lederman MM, Kim RB. Pharmacogenetics of nevirapine-associated hepatotoxicity: an Adult AIDS Clinical Trials Group collaboration. Clin Infect Dis. 2006; 43(6): 783-6. **PubMed** | **Google Scholar**

16. Omoregie R, Omokaro EU, Palmer O, Ogefere HO, Egbeobauwaye A, Adeghe JE, Osakue SI, Ihemeje V. Prevalence of anaemia among HIV-infected patients in Benin City, Nigeria. Tanzan J Health Res. 2009; 11(1): 1-4. **PubMed** | **Google Scholar**

17. World Health Organisation (Daniel J. Raiten, Steven Grinspoon and Stephen Arpadi). **Nutritional considerations in the use of ART in resource use of ART in resource-limited settings limited settings**. 2005. Accessed 6 November 2017

Table 1: General characteristics of study participants			
Variable	**Patients on cART**	**cART naïve patients**	**P-value**
	(N = 65)	(N = 45)	
Age (years)(Mean± SD)	41.6 ± 13.58	42.4 ± 15.4	0.767
Gender			
Male (n (%)	19 (29.2)	18 (40.0)	0.24
Female (n (%)	46 (70.8)	27 (60.0)	
Age group			
< 30	7 (10.8)	6 (13.3)	0.863
30-39	23 (35.4)	12 (26.7)	
40-49	19 (29.2)	16 (35.6)	
50-59	10 (15.4)	6 (13.3)	
≥ 60	6 (9.2)	5 (11.1)	
PT (sec.)	13.8 ± 2.05	17.2 ± 4.24	**<0.001***
APTT (sec.)	55.3 ± 11.8	59.7 ± 14.5	0.081
Platelets (×10^3/mm^3)	204.7 ± 62.9	193.6 ± 75.7	0.402
WBC ×10^3/mm^3	3.9 ± 1.5	4.0 ± 1.2	0.605
INR	1.2 ± 0.2	1.44 ± 0.4	**<0.001***
*P< 0.05, **PT**= Prothrombin Time, **APTT**= Activated Partial Thromboplastin Time, **WBC**=White Blood Cells, **INR**= International Normalized Ratio			

Table 2: Coagulation profile of study participants			
Variable	**Patients on cART**	**cART naïve patients**	***P*-value**
	(N = 65) n (%)	(N = 45) n (%)	
***PT* (sec.)**			
< 10	1 (1.5)	0 (0.0)	0.403
10-15	49 (75.4)	15 (33.3)	< 0.001
> 15 *APTT* (sec.)	15 (23.1)	30 (66.7)	< 0.001
25-45	14 (21.5)	6 (13.3)	0.273
> 45 *Platelets(×10^3/mm^3)*	51 (78.5)	39 (86.7)	0.273
< 150	12 (18.5)	12 (26.7)	0.306
150-400	53 (81.5)	32 (71.1)	0.200
> 400	0 (0.0)	1 (2.2)	0.227

Table 3: Coagulation profile of study participants on cART stratified by the type of cART combination				
Parameter	**CB1**	**CB2**	**CB3**	***P*-value**
	(N = 27)	(N = 27)	(N = 11)	
PT (sec.)	13.24 ± 1.48	14.66 ± 2.35*	13.23 ± 1.92	0.020
APTT (sec.)	56.81 ± 9.22	56.85 ± 11.91	47.55 ± 15.08	0.058
Platelets (×10^3/mm)	211.44 ± 75.80	197.74 ± 48.63	205.46 ± 63.22	0.732
WBC(×10^3/mm^3)	3.68 ± 1.27	3.99 ± 1.87	4.18 ± 0.32	0.588
INR PT n (%)	1.10 ± 0.12	1.22 ± 0.20*	1.10 ± 0.16	0.020
< 10	1 (3.7)	0 (0.0)	0 (0.0)	0.489
10-15	24 (88.9)	16 (59.3)	9 (81.8)	0.035
> 15 APTT (sec.)	2 (7.4)	11 (40.7)	2 (18.2)	0.013
25-45	3 (11.1)	4 (14.8)	7 (63.6)	<0.001
> 45 Platelets(×10^3/mm)	24 (88.9)	23 (85.2)	4 (36.4)	<0.001
< 150	7 (25.9)	3 (11.1)	2 (18.2)	0.374
150-400	20 (74.1)	24 (88.9)	9 (81.8)	0.374
> 400 WBC (×10^3/mm^3)	0 (0.0)	0 (0.0)	0 (0.0)	
< 4	17 (63.0)	16 (59.3)	3 (27.3)	0.116
4-10	10 (37.0)	10 (37.0)	8 (72.7)	0.093
> 10	0 (0.0)	1 (3.7)	0 (0.0)	0.489
P<0.05, *significantly different from group on **CB1** (Combination 1),CB1= AZT+LAM+EFV, **CB2**= AZT+LAM+NEV, **CB3**= AZT+NEV+EFV				