Original Article

Determinants of Isolated Systolic Hypertension among HIV/AIDS on Highly Active Antiretroviral Therapy: A Cross Sectional Study in the GA South Metropolis

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Abstract

Background: Mortality in HIV/AIDS patients have increasingly been attributed to non-communicable causes. Since the dawn of Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (HIV/AIDS) infection and antiretroviral drugs, there has been conflicting data on the role of Antiretroviral Therapy (ART) use across the globe with no data in Ghana. We studied the prevalence and determinants of isolated systolic hypertension in HIV/AIDS patients on ART. **Method:** This cross-sectional study involved 200 HIV/AIDS patients who received treatment at the HIV/AIDS clinic of the GA South Municipal Hospital in Accra, Ghana. Blood pressure (systolic and diastolic), pulse and anthropometric (weight and height, waist and hip circumference) data were obtained using standard protocols. Other relevant data were obtained with the aid of a pretested questionnaire. **Results:** Age, Blood Pressure, Pulse Pressure, BMI and WHR were significantly associated with duration of ART use. The mean systolic blood pressure was significantly high in patients who have been on ART for over 2 yrs. Males were significantly older than females (p=0.003). 4%, 0.5%, and 5.5% of the participants had grade 1, 2, and ISH respectively. Gender was significantly associated with ISH (p=0.021). Females are less likely to develop isolated systolic hypertension. Those within the age group; 30-39 yrs (OR: 7.05, 95% CI: 4.10-12.13, p<0.0001), 40-49 yrs (OR: 3.42, 95% CI: 0.36-32.10, p<0.0001) 50-59 yrs (OR: 6.13, 95% CI: 0.62-61.03, p<0.0001) are at risk of developing ISH. **Conclusion:** Isolated systolic hypertension was prevalent in 5.5% of HIV/AIDS patients on ART. Age and gender were the significant determinants of ISH. Efficient and easy accessible measures should be adopted to prevent and control ISH in HIV/AIDS patients on ART especially males and young adults.

Keywords: Human Immunodeficiency Virus infection and Acquired Immune Deficiency Syndrome (HIV/AIDS); Isolated Systolic Hypertension(ISH); Antiretroviral Therapy (ART); Pulse Pressure (PP); Body Mass Index (BMI); Waist: Hip ratio (WHR)

Introduction

Human Immuno Deficiency Virus infection and Acquired Immune Deficiency Syndrome (HIV/AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus. [1] HIV infects cells of the immune system, destroying or impairing their function. Infection with the virus results in progressive deterioration of the immune system, leading to immune deficiency. According to estimates by WHO and UNAIDS, 36.7 million people were living with HIV globally at the end of 2015. Sub-Saharan Africa is the most affected region, with 25.6 million which accounts for two-thirds of the global total of new HIV infections. 1.1 million persons living with HIV died of HIV-related causes globally. [2] The National HIV/AIDS estimates in 2014 showed Ghana had 250,232 persons living with HIV with 59% being females and 41% males. 229,009 accounting for 92% were adults and 21,223 (8%) were children. A total of 11,356 new infections and 9,248 AIDS-related deaths were recorded in 2014. [3]

Highly Active Antiretroviral Therapy (HAART) regimen was introduced worldwide in 1996 as a way of treatment to prevent viral resistance which has been the case with ordinary antiretroviral medicines. [4] The use of HAART impairs residual levels of viral replication in blood to undetectable levels. Access to HAART has significantly reduced the rate of HIV infection-related mortality and morbidity. [5] However, new concerns have arisen regarding the adverse effects of HAART. Due to the adverse metabolic effects such as increased blood pressure and dyslipidemia, associated with HAART regimen, there have been reported cases of increased incidences of cardiovascular disorders in PLHIV.

Using HAART in HIV infection management has led to increased prevalence hypertension [6] and arterial stiffness. [7] According to JNC-VI WHO/ISH, Isolated systolic hypertension (ISH), is defined as systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) <90 mmHg. Pulse Pressure in older subjects represents a surrogate measurement of central elastic artery stiffness in the presence of a constant cardiac output and heart rate. Thus, the central

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arterial stiffening is manifested by a rise in pulse pressure leading to a rise in SBP and a fall in DBP, ultimately resulting in Isolated Systolic Hypertension. [8]

Mortality in HIV/AIDS patients have increasingly been attributed to non-communicable causes. [9] Since the dawn of HIV/AIDS infection and antiretroviral drugs, there has been conflicting data on the role of Antiretroviral Therapy (ART) use across the globe with no data in Ghana. We studied the prevalence and determinants of isolated systolic hypertension in HIV/AIDS patients on ART in the GA South metropolis of Accra, Ghana.

Materials and Methods

Study design and study site

This cross-sectional study was carried out at the HIV/AIDS clinic of the GA South Municipal Hospital in Accra, Ghana. GA South Municipal is one of the ten districts in Greater Accra Region. It lies within Latitude 5° 48 North 5° 29 North and Latitude 0° 8' West and 0° 30' West. The total land area is estimated at 517.2 sq/km with about 362 communities. Its projected population for 2012 was 316,091.

Participants

The study involved 200 HIV/AIDS patients who received treatment at the HIV/AIDS clinic of the GA South Municipal Hospital within the period for the study. To determine the required sample size, the formula: $n=Z^2PQ/d^2$ was used, where, Z=1.96, P=prevalence of HIV in Ghana i.e., 0.015; [3] Q=1-P i.e., 0.985 and d=margin of error i.e., 0.05. Thus, the calculated sample size was n=23. To account for potential non-response, 200 participants were recruited for the study. A pretested questionnaire was used to collect participants' demographic and clinical data including ART regimen, period of ART use, ART side effect naivety, presence or absence of HIV related-comorbidity and the treatment of such comorbidity. The authorities at the GA South Municipal Hospital and the Institutional Review Board of University of Cape Coast (UCCIRB) approved the study. Informed written consent was sought from the participants before obtaining their data.

Inclusion criteria/Exclusion criteria

HIV positive patients who were on consistent HAART regimen and have not been diagnosed of hypertension prior to commencing antiretroviral therapy were included in the study. HIV positive patients with other HIV related-comorbidities were included in the study. HIV negative patients were excluded. HIV positive patients already diagnosed of hypertension were excluded. ART naïve HIV/AIDS positive patients were excluded from the study.

Anthropometric measurements

The height (to the nearest cm) and weight (to the nearest Kg) were measured with a SECA body meter and a weighing balance (Hospibrand ZT-120, England). The height was taken without the patient wearing footwear and the weight measured wearing light clothing. The Body Mass Index (BMI) was then calculated by dividing weight (Kg) by height squared (m^2) and categorized according to WHO criteria into normal weight (BMI 18.5–24.9), underweight (<18.5), overweight (25.0–29.9), obese (>30.0). Waist and hip circumference was measured to the nearest 0.1 (cm) using non-stretchable tape body. Participants asked to stand still with heels together and their waist circumference (WC) was obtained by measuring the distance around the smallest area below the rib cage and above umbilicus (belly button). Hip circumference measurements were taken at the point yielding the maximum circumference over the buttocks with the tape in a horizontal plane, touching but not compressing the skin. Waist-hip ratio was determined by dividing waist circumference (cm) to hip circumference (cm). Abnormal waist circumference (abdominal obesity) was defined as WC ≥ 102 (cm) for males and WC ≥ 88 (cm) for females. Abnormal waist-hip ratio (WHR) was defined as WHR ≥ 0.9 for males and WHR ≥ 0.85 for females.

Blood pressure was measured twice by a trained staff nurse at the hospital using a mercury sphygmomanometer and a stethoscope (Accoson Dekamet, England), after patients had rested for at least 15 minutes. This was done in accordance with the recommendations of the American Heart Association. [10] Average of each systolic and diastolic pressure was estimated. Blood pressures of all respondents were measured in a sitting position on the right upper arm. Pulse pressure was calculated from the blood pressure measured.

Hypertension status was categorized as: optimal (SB*P*<120, DB*P*<80); normal (SBP= 120-129, DBP= 80-84); high-normal (SBP=120-139 or DBP=80-89); Stage 1 hypertension (SBP=140-159 or DBP=90-99); Stage 2 hypertension (SBP >160 or DBP>100); ISH (SBP ≥ 140, DB*p*<90). [11] All anthropometric measurements were performed twice separately and then the average of the two readings was recorded.

Table 1: Demographics and clinical characteristics of HIV patients on ART in relation to duration on ART.

Variables	Duration on ART		p-value
	≤ 2 years (n=100)	> 2 years (n=100)	
Age (years)	40.25 ± 10.35	43.57 ± 9.43	**0.019**
Gender			0.279
Male	22 (22.0)	16 (16.0)	
Female	78 (78.0)	84 (84.0)	
Age group n (%)			**0.010**
20-29	18 (18.0	3 (3.0)	
30-39	30 (30.0)	34 (34.0)	
40-49	31 (31.0)	39 (39.0)	
50-59	17 (17.0)	16 (16.0)	
60-69	4 (4.0)	8 (8.0)	
Presence of comorbidity			1.000
Yes	6 (6.0)	6 (6.0)	
No	94 (94.0)	94 (94.0)	
Treatment for comorbidity			0.801
Yes	4 (4.0)	5 (5.0)	
No	2 (2.0)	1 (1.0)	
Naïve of ART side effect			**0.002**
Yes	11 (11.0)	28 (28.0)	
No	89 (89.0)	72 (72.0)	
Type of ART			0.561
NNRTI+NRTI	99 (99.0)	98 (98.0)	
PI+NRTI	1 (1.0)	2 (2.0)	
Blood pressure (mmHg)			
SBP	109.30 ± 11.74	118.10 ± 14.89	**<0.0001**
DBP	73.20 ± 10.43	77.20 ± 11.90	**0.012**
Pulse	36.40 ± 10.59	40.70 ± 11.83	**0.007**
BMI (Kg/m²)	19.01 ± 3.62	20.44 ± 4.47	**0.014**
BMI n (%)			**0.106**
Underweight	48 (48.0)	43 (43.0)	
Normal	46 (46.0)	40 (40.0)	
Overweight	4 (4.0)	13 (13.0)	
Obese	2 (2.0)	4 (4.0)	
WC	76.89 ± 10.67	82.71 ± 11.83	**<0.0001**
WHR	0.83 ± 0.05	0.85 ± 0.05	**0.011**

ART: Antiretroviral; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI: Nucleotide Reverse Transcriptase Inhibitors; PI: Protease Inhibitor; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; WC: Waist Circumference; WHR: Waist: Hip Ratio

Table 2: Age distribution and clinical characteristics of HIV patients on ART in relation to gender.

Variables	Total (n=200)	Male (n=38)	Female (n=162)	p-value
Age (years)	41.91 ± 10.02	46.21 ± 8.12	40.90 ± 10.17	**0.003**
Age group n (%)				**0.006**
20-29	21 (10.5)	1 (4.8)	20 (95.2)	
30-39	64 (32.0)	5 (7.8)	59 (92.2)	
40-49	70 (35.0)	21 (30.0)	49 (70.0)	
50-59	33 (16.5)	8 (24.2)	25 (75.8)	
60-69	12 (6.0)	3 (25.0)	9 (75.0)	
Presence of comorbidity				0.585
Yes	12 (6.0)	3 (25.0)	9 (75.0)	
No	188 (94.0)	35 (18.6)	153 (81.4)	
Treatment of commodity				0.787
Yes	9 (4.5)	2 (22.2)	7 (77.8)	
No	3 (1.5)	1 (33.3)	2 (66.7)	
Naïve of ART side effect				0.273
Yes	39 (19.5)	5 (12.8)	34 (87.2)	
No	161 (80.5)	33 (20.5)	128 (79.5)	
Type of ART				0.398
NNRTI+NRTI	197 (98.5)	38 (19.3)	159 (80.7)	
PI+NRTI	3 (1.5)	0 (0.0)	3 (100)	
Blood pressure (mmHg)				
SBP	113.70 ± 14.08	117.37 ± 13.69	112.84 ± 14.07	0.074
DBP	75.20 ± 11.34	75.53 ± 10.83	75.12 ± 11.49	0.844
Pulse	38.55 ± 11.40	41.58 ± 11.75	37.84 ± 11.24	0.069
BMI (Kg/m²)	19.73 ± 4.12	20.47 ± 4.83	19.55 ± 3.93	0.214
BMI n (%)				0.228
Underweight	91 (45.5)	13 (14.3)	78 (85.7)	
Normal	86 (43.0)	21 (24.4)	65 (75.6)	
Overweight	17 (8.5)	2 (11.8)	15 (88.2)	
Obese	6 (3.0)	2 (33.3)	4 (66.7)	
WC	79.80 ± 11.61	82.34 ± 12.47	79.20 ± 11.36	0.134
WHR	0.84 ± 0.05	0.84 ± 0.05	0.84 ± 0.05	0.798

ART: Antiretroviral; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI: Nucleotide Reverse Transcriptase Inhibitors; PI: Protease Inhibitor; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; WC: Waist Circumference; WHR: Waist: Hip Ratio

Table 3: Hypertension among HIV patients on ART.

Blood pressure categories	Systolic	Diastolic	Frequency (n=200)	Percentage (%)
Optimal	<120	<80	92	46.0
Normal	120-129	80-84	14	7.0
Prehypertension	130-139	85-89	0	0.0
Hypertension				
Grade 1	140-159	90-99	8	4.0
Grade 2	160-179	100-109	1	0.5
Isolated Systolic	≥ 140	≤ 90	11	5.5

Statistical analysis

Results are expressed as means ± SD. Unpaired t-test was used to compare mean values of continuous variables and $\chi 2$ test statistic for all categorical variables. Logistics regression analysis was used to determine the risk factors associated with isolated systolic hypertension among HIV patients on ART. For all statistical comparisons, a $p<0.05$ was considered as statistically significant. Analyses and statistical procedures were carried out using the Statistical Package for Social Sciences program (SPSS, version 21.0 for Windows).

Table 4: Age distribution and clinical characteristics stratified by isolated systolic hypertension of HIV patients on ART.

Variables	Isolated Systolic Hypertension		p-value
	Yes (n=11)	No (n=189)	
Gender			**0.021**
Male	5 (45.5)	33 (17.5)	
Female	6 (54.5)	156 (82.5)	
Age (years)	47.36 ± 8.37	41.59 ± 10.03	0.063
Age group n (%)			0.167
20-29	0 (0.0)	21 (11.1)	
30-39	1 (9.1)	63 (33.3)	
40-49	5 (45.5)	65 (34.4)	
50-59	4 (36.4)	29 (15.3)	
60-69	1 (9.1)	11 (5.8)	
Presence of comorbidities			0.389
Yes	0 (0.0)	12 (6.3)	
No	11 (100)	177 (93.7)	
Naïve of ART side effect			0.910
Yes	2 (18.2)	37 (19.6)	
No	9 (81.8)	152 (80.4)	
Type of ART			0.674
NNRTI+NRTI	11 (100)	186 (98.4)	
PI+NRTI	0 (0.0)	3 (1.6)	
Pulse	56.36 ± 8.09	37.51 ± 10.70	**<0.0001**
Years on ART			0.121
≤2	3 (27.3)	97 (51.3)	
>2	8 (72.7)	92 (48.7)	
BMI (Kg/m²)	21.09 ± 4.39	19.65 ± 4.10	0.259
BMI n (%)			0.110
Underweight	3 (27.3)	88 (46.6)	
Normal	5 (45.5)	81 (42.9)	
Overweight	3 (27.3)	14 (7.4)	
Obese	0 (0.0)	6 (3.2)	
WC	87.09 ± 12.01	79.38 ± 11.48	**0.032**
WHR	0.86 ± 0.06	0.84 ± 0.05	0.207

ART: Antiretroviral; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; NRTI: Nucleotide Reverse Transcriptase Inhibitors; PI: Protease Inhibitor; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; WC: Waist Circumference; WHR: Waist: Hip Ratio

Results

Table 1 shows the association between demographics and clinical characteristics of participants in relation to duration on ART. Age, blood pressure, pulse pressure, BMI and Waist: Hip ratio was significantly associated with duration of ART use. Participants who answered YES to side effect naivety were more of those who have been on ART for over 2 yrs. The mean systolic blood pressure was significantly high in patients who have been on ART for over 2 yrs. Blood Pressure, Pulse Pressure, and Waist: Hip ratio was significantly higher in participants who have been on ART for more than 2 years.

Table 2 shows the age distribution and clinical characteristics of participants on HAART in relation to gender. Males were significantly older than the females (p=0.003). Most of the participants were between the ages of 40-49 yrs. Most of the male participants were between the ages of 40-49 yrs. Most of the females were between 20-29 yrs age group.

Table 5: Determinants of isolated systolic hypertension among HIV patients on ART.

Variables	OR (95% CI)	p-value
Gender		
Male*	1	
Female	0.25 (0.07-0.88)	**0.031**
Age group		
20-29*	1	
30-39	7.05 (4.10-12.13)	**<0.0001**
40-49	3.42 (0.36-32.10)	**<0.0001**
50-59	6.13 (0.62-61.03)	**<0.0001**
60-69		
Naïve of ART side effect		
Yes	0.91 (0.19-4.40)	0.910
No*	1	
Type of ART		
NNRTI+NRTI	2.62×10^7 (2.62×10^7)	-
PI+NRTI*	1	
Years on ART		
≤ 2*	1	
>2	2.81 (0.72-10.92)	0.135
BMI n (%)		
Underweight	0.55 (0.13-2.39)	0.426
Normal*	1	
Overweight	3.47 (0.74-16.19)	0.113
Obese	-	-

*Reference category

Table 3 shows the frequency of hypertension among participants on HAART. 4%, 0.5%, and 5.5% of the participants had grade 1, 2, and Isolated systolic hypertension respectively.

Table 4 shows the age distribution and clinical characteristics of participants stratified by isolated systolic hypertension. Sex was significantly associated with ISH (p=0.021). Participants with ISH had higher pulse pressure and waist circumference.

Table 5 shows the determinants of isolated systolic hypertension among participants on HAART. Females are less likely to develop isolated systolic hypertension. Those within the age group; 30-39 yrs, 40-49 yrs, 50-59 yrs are at 7 times, 3 times, and 6 times at risk of developing ISH.

Discussion

High blood pressure is the most common single risk factor for cardiovascular related events and deaths worldwide. [9] This study sought to examine the prevalence and determinants of isolated systolic hypertension (ISH) in HIV patients on consistent HAART regimen within the GA South Metropolis, Ghana. Antiretroviral usage has been in existence for some years in Ghana, but HAART is relatively a new treatment concept in the health delivery system. [12] As such, information generated locally on the side effects of the drugs involved is based mainly on case reports at the various hospitals. This is the first study to report the prevalence and associated risk factors of ISH among HIV/AIDS patients on consistent HAART regimen in Ghana.

For HIV-infected patients receiving treatment with HAART, it is suspected that the risk for CVD is significantly greater than that for the general population and this is expected to increase with each year of HAART. [12,13] The findings of this study indicate that 5.5% of HIV patients on HAART had isolated systolic hypertension. In a multivariate analysis using logistic regressions, we observed that age and gender were the only significant determinant of ISH after adjusting for age group, gender, naïve of ART side effect, type of ART, years on ART, and BMI. The adjusted odd ratio of having isolated systolic hypertension in those within age group 30-39 years [7.05 (95% CI: 4.10-12.13), $p<0.0001$] 40-49 years [(95% CI: 3.42 (0.36-32.10), $p<0.0001$] and 50-59 years [(95% CI: 6.13(0.62-61.03), $p<0.0001$]. This is in accordance with Dimala et al. [14] who reported age and male gender as the only risk factors significantly associated with HTN in HIV/AIDS patients on HAART. Pulse pressure and waist circumference were significantly higher in ISH which is in consonance with De Socio & Schillaci. [15] Pulse pressure is considered a more sensitive measure of CVD and its increase alongside SBP is as a result of increased arterial stiffness. [15] In middle-aged and older individuals with ISH, PP has been made known to be an independent risk factor for predicting CV events. Indeed, ISH with increased PP has been associated with a variety of CV events. [16]

The prevalence of ISH among PLHIV on HAART observed in this study is slightly lower than that recorded by Fianko [12] during his study in the prevalence of arterial cardiovascular risk factors among HIV patients on HAART in Kumasi South Hospital. Generally, difference in geographical locations, study settings, clinical characteristics of the study population and designs and even the number of variables taken as risk factors, could attribute to the cause of variations in prevalence of ISH. However, it is worth noting that the observed prevalence of ISH could be lower, given the fact that the participants were predominantly females; patients who were already diagnosed with hypertension before being placed on HAART were excluded.

We observed that, there was no significant association between the duration of HAART and ISH. This is on the other hand, contrary to Dimala et al. [14] who suggested a link between the duration of HAART and BP indicating that prolong HAART was independently associated with developing hypertension.

All participants used more than one HAART regimen but there was no significant association between the type of HAART used and development of ISH. This is in accordance with Crane et al who reported no relation between the use of NNRTI or PIs to the development of elevated BP.

Hejazi, Huang, Lin and Choong [17] reported common pathophysiologic pathways between gender, increase in age and bigger waist circumference to the occurrence of hypertension. This is supported by the findings of higher mean WC and age in relation to gender. The difference in prevalence of hypertension between two genders is due to the sex hormones as a pathophysiologic reason. [18]

It is proven that female sex hormones support renal hemodynamics and prevent excessive sodium reabsorption by kidney. Thus salt sensitivity among premenopausal women is less than males. [17,19] In this study male gender was a significant risk factor for ISH which is in agreement with [17,20] who reported male gender as a risk factor for developing systolic hypertension in men on HAART.

ISH has become the most common type of hypertension in the elderly, and the most prevalent type of untreated hypertension among adult over 60 yrs. Aging causes a loss in vessel function by stiffening of the arterial vasculature. The vascular changes include the advanced reduction in visco-elastic properties of vessels, progressive atherosclerotic arterial disease, and hypertrophy/sclerosis of muscular arteries and arterioles which narrow the vessels wall and make a resistance to blood pressure and flow. [21] Although ISH is usually associated with the elderly, there is now strong evidence that ISH is also the majority hypertensive subtype in young adults. McEniery et al., [22] confirmed that persons with ISH outnumbered those with essential hypertension (elevated SBP and DBP, or DBP alone) by a ratio of approximately 2:1. Young adults presenting with ISH had a marked male predominance

with heterogeneous hemodynamic patterns-increased stroke volume, increased aortic stiffness or a combination of both. [16]

The Framingham study and The Multiple Risk Factor Intervention Trial showed that SBP levels are stronger predictors of cerebrovascular and cardiovascular events than DBP. ISH increases cardiovascular morbidity and all-cause mortality two fold or more and triples cardiovascular mortality. [23]

This study however, is limited by its cross-sectional design, restricting any inference about causality and the use of a smaller sample size. Further studies will need to consider the study design and the sample size. Also, this study did not include HIV-negative controls as in other studies. [24] The study did not control for unmeasured potential confounders such as diabetes, renal disease and dyslipidemia.

Conclusion

Isolated systolic hypertension was prevalent in 5.5% of PLHIV on HAART. Age and gender were found to be the major risk factor of ISH. Efficient and easy accessible measures should be adopted to prevent and control ISH in PLHIV on HAART especially males and young adults.

Conflict of Interest

The authors disclose that they have no conflicts of interest.

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