

A profile of blood pressure changes in patients on anti-retroviral treatment in a tertiary health centre in Nigeria

Ajayi, S.^{1,2,4}, Adebisi, A.¹, Mamven, M.³, Dakum, P.⁴

¹Department of Medicine, College of Medicine, University of Ibadan, and University College Hospital, Ibadan, Nigeria

²Department of Clinical Sciences, Nigerian Institute of Medical Research, Lagos, Nigeria

³Department of Medicine, University of Abuja Teaching Hospital, Abuja, Nigeria

⁴Institute of Human Virology, Nigeria, Abuja

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Corresponding author:

Ajayi, S.

ORCID-NO: <https://orcid.org/0000-0003-4395-9222>

soajayi@hotmail.com

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Abstract

Introduction: HIV-infected individuals live longer due to life-saving antiretroviral treatment (ART), their risk for other comorbidities like hypertension increases. Therefore, the risk factors of developing hypertension in these patients may include co-morbidities like obesity and effects of combination anti-retroviral therapy (cART). This study of both cART-naïve and cART-experienced patients aimed to determine the profile of blood pressure changes.

Methods: This was a retrospective analysis of data obtained from HIV care and treatment records at a treatment centre for HIV. To study blood pressure changes over the course of treatment and follow-up and the use of cART, we categorized the study population into three: those who had not been commenced on cART, those who were on cART for up to 1 year, and those who were on cART for more than one year.

Results: There were 6,325 patients with complete data suitable for analysis, of which there were 4,112 females (65%). The levels of all blood pressure phenotypes increased over the treatment period for the study participants. The first and last SBP were higher for patients on cART for more than one year than on patients who were on cART for about one year (110.6(6.07) vs 108.1(15.31) mmHg, $p < 0.001$ and 113.3(15.30) mmHg vs 109.4(15.18) mmHg, $p < 0.001$). The maximum SBP was also highest at 130.9(17.25) mmHg for patients who were on cART for more than one year. Similarly, DBP was higher in those who were on cART for more than 1 year. The mean arterial pressure was also higher, from 83.1(8.03) to 85.7(7.62) mmHg ($p < 0.001$).

Conclusion: The blood pressure phenotypes showed a consistent increase in those who were on cART for more than one year compared to those on cART for 1 year or less.

Un profil des changements de tension artérielle chez les patients sous traitement antirétroviral dans un centre de santé tertiaire au Nigeria

Resume

Introduction: Les personnes infectées par le VIH vivent plus longtemps grâce au traitement antirétroviral (TAR) qui leur sauve la vie, et leur risque d'autres comorbidités comme l'hypertension augmente. Par conséquent, les facteurs de risque de développer une hypertension chez ces patients peuvent inclure des comorbidités telles que l'obésité et les effets de la thérapie antirétrovirale combinée (TARc). Cette étude portant à la fois sur des patients naïfs et expérimentés sous TARc visait à déterminer le profil de la pression artérielle. changements.

Méthodes: Il s'agissait d'une analyse rétrospective des données obtenues à partir des dossiers de soins et de traitement du VIH dans un centre de traitement du VIH. Pour étudier les changements de tension artérielle au cours du traitement, du suivi et de l'utilisation du TARc, nous avons classé la population étudiée en trois catégories : celles qui n'avaient pas commencé à prendre un TARc, celles qui étaient sous TARc depuis moins d'un an et celles qui n'avaient pas encore commencé à prendre un TARc. qui étaient sous TARc depuis plus d'un an.

Résultats : Il y avait 6 325 patients avec des données complètes pouvant être analysées, dont 4 112 femmes (65 %). Les niveaux de tous les phénotypes de tension artérielle ont augmenté au cours de la période de traitement pour les participants à l'étude. La première et la dernière PAS étaient plus élevées chez les patients sous TARc depuis plus d'un an que chez les patients sous TARc depuis environ un an (110,6 (6,07) contre 108,1 (15,31) mmHg, $p < 0,001$ et 113,3 (15,30) mmHg contre 109,4. (15,18) mmHg, $p < 0,001$). La PAS maximale était également la plus élevée à 130,9 (17,25) mmHg pour les patients sous TARc pendant plus d'un an. De même, le DBP était plus élevé chez ceux qui suivaient un TARc pendant plus d'un an. La pression artérielle moyenne était également plus élevée, de 83,1(8,03) à 85,7(7,62) mmHg ($p < 0,001$).

Conclusion: Les phénotypes de tension artérielle ont montré une augmentation constante chez ceux qui étaient sous TARc pendant plus d'un an par rapport à ceux sous TARc pendant 1 an ou moins.

INTRODUCTION

Human immunodeficiency virus (HIV) infection is expected to escalate the burden of disease in those infected because, in many of these individuals, the prevalence and incidence of other co-morbidities may also increase. This may especially be the case because patients living with HIV now live longer since the advent of the combination anti-retroviral therapy (cART). Therefore, the risk factors of developing hypertension in these patients may include obesity, genetic predisposition, effects of cART, and immune and inflammatory changes from HIV infection (1). Furthermore, important life style modifications in prevention and control of hypertension may be problematic because of the added burden of a disease that, in many developing countries, carries a considerable stigma and exerts financial difficulties. Inadequate access to healthcare and poor health infrastructure in many developing and resource-poor countries, especially in sub-Saharan Africa, are known to compound care of patients (2,3). Therefore, compared to HIV-negative individuals, hypertension, the commonest risk factor for cardiovascular disease worldwide may be common, under-diagnosed and under-reported in HIV infected persons as was previously reported (4). These patients, because of the complex social and medical issues involved in coping and managing this disease (5), may have poor awareness and motivation to care about non-communicable diseases like hypertension (6).

Some of the anti-retroviral medications are known to have significant metabolic side effects that may be involved in the pathogenesis of hypertension or complicate its control. These include protease inhibitors (Pis) and certain non-nucleoside reverse transcriptase inhibitors (NNRTIs). The pathophysiological mechanisms may include their effects on endothelial function and dysregulation of the immune system, both implicated in the etiopathogenesis of hypertension (1). These mechanisms include T-cell activation and cytokine release leading to sodium and water retention (7). Before initiation of therapy, HIV infected patients are less overweight than HIV-negative patients, but there is evidence that weight gain increases during therapy and care. This may result in the development of hypertension. Adiposity is also a risk factor for metabolic diseases like diabetes mellitus and insulin resistance. Furthermore, activation of the renin-angiotensin aldosterone system (RAAS) occurs in patients with HIV and may contribute to the pathogenesis (8).

Therefore, these traditional risk factors may become overt and play significant role in the development of hypertension.

Nigeria, with a population of over 190 million people, and a prevalence of 3% has more than 3 million HIV infected persons (9). This makes the country to have the second highest burden of HIV globally. Nigeria began a rapid scale up of ART in the early 2000s. This was made possible by efforts of the government and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR). The prevalence of hypertension in HIV-infected persons has been reported to be between 13.3 and 26.7% (10,11). Thus, there is a huge burden of hypertension among PLHIV in Nigeria.

Many of the studies on hypertension were cross-sectional or involved ARV-naïve patients, thereby not adequately robust to identify meaningful risk factors or characterize the role of antiretroviral medications in pathogenesis. It is therefore pertinent to explore the risk factors of hypertension in HIV infected patients, with a view to promoting prevention and management of this co-morbidity. This longitudinal study of both ARV-naïve and ARV-experienced patients aimed to determine the profile of blood pressure changes in patients with HIV infection.

MATERIALS AND METHODS

The PEPFAR supports the University of Abuja Teaching Hospital through the Institute of Human Virology, Nigeria's AIDS Care and Treatment in Nigeria (ACTION) programme. The ACTION programme supports free counselling, diagnosis, treatment, home-based care, adherence counselling, and nutritional support for patients with HIV. This has enabled thousands of patients to access comprehensive care for HIV. Between 2005 and 2013, the period under review, at least 13,000 patients were under care, either receiving ARVs or being monitored prior to receiving ARVs. Only adult patients, 18 years and older, were included in this analysis.

Patients were seen in a purpose-built facility within the hospital premises, and designated as *ART Clinic*. All staff including nurses, community health workers, data entry officers, monitoring and evaluation officers, records officers, adherence officers, and doctors were specifically employed and trained both centrally for ACTION sites and locally for the thematic areas of care. Manuals and standard operating procedures were provided, and summaries as cards were pasted on boards in critical areas of the clinic.

At enrolment, a standardized case report form was used to document patients' demographic information, weight, height, and blood pressure measurements..

Weights were done with light clothing and without shoes, and heights standing erect. Weights were read in kilogramme and heights in centimetres. A stadiometer was used. Body mass index was calculated using weight and height in kg/m^2 . Mercury sphygmomanometer, Accoson, was used for all blood pressure measurements and nurses who had previously been trained on the programme did all the blood pressure measurements.

Also, either as initial assessment or for monitoring at follow-up, blood samples were taken for CD4 count.

Blood pressure was obtained from patient's records. Hypertension was defined as systolic blood pressure (SBP) $\geq 140\text{mmHg}$ and/or diastolic blood pressure $\geq 90\text{mmHg}$, according to The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report and ESH guidelines (12, 13).

To study blood pressure changes over the course of treatment and follow-up and the use of cART, we categorized the study population into three: those who had not been commenced on cART, those who were on cART for up to 1 year, and those who were on cART for more than one year. At any point in time during the follow-up period, patients who developed hypertension were referred for specialist care. The variables considered were the initial measurement, the minimum, and the maximum blood pressure. The first blood pressure assessment considered to be within the range of hypertension was also documented.

We calculated the time patients stayed under care in the three categories based on the first date of assessment to the last day documented in the records. At the early stage of antiretroviral treatment in Nigeria, patients were commenced on cART when the CD4 count was below 200cells/ μl .

Data and statistical analysis

Data were imported into Microsoft Excel from Careware, a free, electronic health and social support information system for Human Resource and Services Administration 's Ryan White HIV/AIDS Program in 2000(14). After cleaning, data was exported to R version 4.1.0 for analysis (15). Patient population was categorized

into three: those who were not on cART, those who were on cART for up to a year and those who were on cART for more than 1 year in order to explore the effects of cART on blood pressure.

Categorical variables were presented as frequencies with percentages, while continuous variables were presented as mean with standard deviation for normally distributed variables and median with median absolute deviation (mad) for non-normal variables. Coefficient of variations were calculated to explore the relative dispersion of the mean and standard deviation. The differences in the means between the groups of patients were compared with Kruskal-Wallis while Chi-squared analysis was used to compare proportions.

RESULTS

There were 6,325 patients with complete data suitable for analysis, of which there were 4,112 females (65%). (Table 1.) Only 448 participants were not on cART, and the majority were on cART for more than 1 year. The mean weight of participants was 64.7(13.39) kg, and the mean BMI was 24.5(4.69) kg/m^2 . The mean SBP and DBP were 110.4(16.02) mmHg and 72.3(11.25) mmHg, respectively. Patients' CD4 count increased from median of 204(167.53) cells/ mm^3 to a maximum of 488.0(262.42) cells/ mm^3 . (Table 1.)

On the use and duration of use of cART, more females were on cART, and when commenced on cART, were more likely to be on cART for more than 1 year. (Table 1). Though all patients were relatively young, patients on cART for more than 1 year were a little older (36.7(8.72) years). The SBP of patients who were not on cART was 112.3(16.43) mmHg and this was higher than those on cART for more than 1 year, though there was increase of SBP when patient stayed on cART for more than 1 year. The mean diastolic blood pressure showed a similar pattern with an increase when patients stayed on cART for more than 1 year. The BMI of patients were more likely to be higher for patients who were on cART for more than 1 year, compared to those of up to one year (24.8(4.64) kg/m^2 vs 22.8(4.58) kg/m^2 . (Table 1).

The levels for all blood pressure phenotypes increased over the treatment period in this study. The first and last SBP were higher for patients on cART for more than one year than inpatients who were on cART for about one year (110.6(16.07) vs 108.1(15.31) mmHg, $p < 0.001$ and 113.3(15.30) mmHg vs 109.4(15.18) mmHg, $p < 0.001$). (Table 2.) The maximum SBP was also

highest at 130.9(17.25) mmHg for patients who were on cART for more than one year. There was also a similar increase in DBP in those who were on cART for more than 1 year. The mean arterial pressure increased from 83.1(8.03) to 85.7(7.61) mmHg ($p<0.001$), $p<0.001$.

DISCUSSION

In this study of a large ART programme, there were more female patients than males, and most of the patients were on antiretrovirals. They were predominantly young people, though males were older than females. Though the mean blood pressure of cART naïve individuals was higher than for those on cART for about one year, the blood pressure phenotypes showed a consistent increase in those who were on cART for more than one year.

HIV infection has been generally documented to show gender disparity, with more females affected especially in sub-Saharan Africa (16-19). Various reasons have been adduced for this, including a better health seeking behaviour by women and the fact that women in traditional settings have little bargaining power (18,20). Since the availability of ARVs and the widespread counselling and testing prior to the scale-up of ART, women were more likely to be persuaded than men to be in HIV care generally. Furthermore, women were more likely to be diagnosed and enrolled for care because of Prevention of Mother to Child Transmission (PMTCT) of HIV programme. Majority of the patients were young, as reported in previous studies (16,18), and this contributes to the economic burden of disease. Also, development of hypertension in this age group adds significantly to the burden of disease. Hypertension is the most common cause of cardiovascular disease morbidity and mortality globally (21), and more so in resource poor settings with inadequate health infrastructure.

Many more people live longer with HIV now than before because of the improvement in care and availability of cART. Therefore, it is expected that there would be an increase in the co-morbidity of HIV and non-communicable disease. Our study has demonstrated that with increase in time under treatment with cART, there was an increase in blood pressure, indeed for virtually all blood pressure phenotypes. This finding has been documented in previous studies (22), though there have been conflicting reports about whether cART contributes to higher blood pressure (23,24). The mean blood pressure among cART naïve patients was higher than for

those on short term use of cART, but with an increase in duration of being under care, there was an increase in blood pressure. This, perhaps, has accounted for the conflicting report about the use of cART and development of hypertension. One explanation for comparable blood pressure between those who were cART naïve and those who have been on cART for more than one year may be the similarity in their clinical conditions. Patients who were cART naïve were generally well. The small sample size of cART naïve patients may also mean that the relatively higher blood pressure in this group was overestimated.

There was clearly an increase in blood pressure among those on cART for more than one year compared to those on cART for a year or less. This is consistent with previous reports (24-26). This increase may be due to metabolic effects of cART or change in lifestyle of the patients as they get better, and this can be seen in the relative increase in CD4 count of patients on cART, CD4 count being a measure of immunological improvement. It is also to be noted that the population of patients on cART for more than a year is very large compared to the other groups. In population studies, a small increase in blood pressure is quite significant. The mean arterial pressure is significantly higher in this group.

Strengths of this study include the large sample size, the relatively long duration of care, and the detailed clinical parameters available to explore the blood pressure changes. A limitation of the study is that it is a retrospective study, in which it was not possible to systematically set up the study to avoid the confounders such as relationship between increase in BMI and the pressure changes.

CONCLUSION

We found an increase for all blood pressure phenotypes in patients who were on cART for more than 1 year compared to those on cART for a year or less.

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Author's contribution: SA conceived and designed the study, collected the data, performed the analysis and drafted the manuscript. AA designed the study, performed the analysis, and reviewed the draft, and approved it. MM designed the study, reviewed the draft, and approved it. PD obtained funding, contributed data, reviewed the manuscript, and approved it.

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Table 1. Demographic and clinical characteristics of patients

Characteristic	Total N = 6,325 ¹	Not on cART N = 448 ¹	On cART Up to 1 year N = 808 ¹	On cART more than 1 year N = 5,069 ¹	p-value
Gender					0.186
Female	4,112 (65.0%)	307 (68.5%)	534 (66.1%)	3,271 (64.5%)	
Male	2,213 (35.0%)	141 (31.5%)	274 (33.9%)	1,798 (35.5%)	
Age (years)	36.2 (8.74)	33.5 (8.36)	34.6 (8.60)	36.7 (8.72)	<0.001
Weight (kg)	64.7 (13.39)	63.7 (13.98)	59.5 (12.84)	65.6 (13.23)	<0.001
Height (cm)	162.7 (9.23)	163.3 (9.44)	162.6 (8.09)	162.7 (9.36)	<0.001
Height (cm)	163.1 (8.08)	163.5 (8.70)	162.9 (7.49)	163.1 (8.13)	<0.001
Body Mass Index (kg/m ²)	24.5 (4.69)	24.8 (5.01)	22.8 (4.58)	24.8 (4.64)	<0.001
First CD4 count (cells/ μ l)	204.0 (167.53)	447.0 (185.32)	225.0 (191.26)	187.0 (146.78)	<0.001
Last CD4 count (cells/ μ l)	366.0 (217.94)	398.0 (194.22)	266.0 (189.77)	380.0 (219.42)	<0.001
Minimum CD4 count (cells/ μ l)	149.0 (112.68)	288.0 (131.95)	159.0 (117.13)	139.0 (103.78)	<0.001
Maximum CD4 count (cells/ μ l)	488.0 (262.42)	606.0 (255.01)	338.0 (250.56)	500.0 (259.46)	<0.001
Average CD4 count (cells/ μ l)	324.4 (169.54)	445.3 (158.14)	257.3 (164.82)	323.1 (165.94)	<0.001
Number of CD4 count measurements	6.5 (3.33)	6.2 (3.46)	4.0 (3.17)	7.0 (3.15)	0.017
Interval of CD4 measurements	33.8 (19.67)	25.0 (16.64)	14.1 (15.09)	37.7 (18.41)	0.041

¹n (%); Mean (SD); Median (mad)**Table 2. Blood pressure measurements and duration of follow up on cART**

Characteristic	Overall, N = 6,325 ¹	None, N = 448 ¹	Up to 1 year, N = 808 ¹	More than 1 year, N = 5,069 ¹	p- value ²
No of BP measurements	13.9 (6.49)	8.5 (3.88)	8.2 (3.68)	15.3 (6.28)	<0.001
First Systolic BP measurement (mmHg)	110.4 (16.03)	112.3 (16.43)	108.1 (15.31)	110.6 (16.07)	<0.001
Last Systolic BP measurement (mmHg)	112.5 (15.38)	109.9 (15.70)	109.4 (15.18)	113.3 (15.30)	<0.001
Mean Systolic BP (mmHg)	111.5 (10.33)	111.7 (11.93)	108.4 (10.58)	112.0 (10.05)	<0.001
Standard Deviation of Systolic BP (mmHg)	10.6 (3.91)	10.2 (4.78)	10.2 (4.19)	10.7 (3.77)	<0.001
Maximum Systolic BP (mmHg)	129.6 (17.33)	126.5 (18.22)	123.0 (15.61)	130.9 (17.25)	<0.001
First Diastolic BP measurement (mmHg)	72.3 (11.25)	73.5 (11.93)	71.0 (10.85)	72.4 (11.23)	<0.001
Last Diastolic BP measurement (mmHg)	72.0 (10.94)	70.6 (10.97)	70.9 (10.77)	72.3 (10.94)	<0.001
Mean Diastolic BP (mmHg)	72.2 (6.76)	72.4 (7.83)	70.4 (7.06)	72.5 (6.56)	<0.001
Standard Deviation of Diastolic BP (mmHg)	7.9 (2.57)	7.7 (3.26)	7.8 (3.09)	7.9 (2.41)	<0.001
Maximum Diastolic BP (mmHg)	85.3 (10.77)	83.3 (11.75)	81.5 (10.54)	86.0 (10.57)	<0.001
First Mean Arterial BP measurement (mmHg)	85.0 (12.16)	86.4 (12.81)	83.3 (11.50)	85.1 (12.19)	<0.001
Last Mean Arterial BP measurement (mmHg)	85.5 (11.66)	83.7 (11.94)	83.7 (11.42)	86.0 (11.64)	<0.001
Mean Arterial BP (mmHg)	85.3 (7.82)	85.5 (9.04)	83.1 (8.03)	85.7 (7.61)	<0.001
Standard Deviation of Mean Arterial BP (mmHg)	8.1 (2.76)	7.9 (3.45)	7.9 (3.05)	8.1 (2.63)	<0.001
Maximum Mean Arterial BP (mmHg)	99.2 (12.01)	97.1 (13.23)	94.7 (11.23)	100.1 (11.83)	<0.001
First Pulse Pressure measurement (mmHg)	38.1 (9.95)	38.9 (9.63)	37.1 (10.49)	38.2 (9.88)	0.002
Last Pulse Pressure measurement (mmHg)	40.6 (10.08)	39.3 (9.42)	38.6 (10.33)	41.0 (10.05)	<0.001
Mean Pulse Pressure (mmHg)	39.3 (4.68)	39.3 (5.42)	38.0 (5.26)	39.5 (4.47)	<0.001
Maximum Pulse Pressure (mmHg)	53.2 (11.68)	50.1 (11.17)	49.0 (10.50)	54.1 (11.71)	<0.001
Follow-up Duration (months)	37.1 (19.54)	25.6 (15.75)	16.9 (14.89)	41.3 (18.03)	<0.001
Coefficient of variation of Systolic BP (%)	9.4 (3.01)	9.0 (3.63)	9.4 (3.55)	9.4 (2.85)	<0.001
Coefficient of variation of Diastolic BP (%)	10.9 (3.15)	10.6 (3.93)	11.0 (4.06)	10.9 (2.89)	0.007
Coefficient of variation of Mean Arterial BP (%)	9.4 (2.79)	9.1 (3.47)	9.4 (3.35)	9.4 (2.62)	0.005
Coefficient of variation of Pulse Pressure (%)	20.2 (6.90)	19.5 (7.69)	20.6 (8.80)	20.2 (6.46)	0.026
Duration of CART use (months)	35.8 (20.38)	0.0 (0.00)	7.3 (3.36)	40.8 (17.77)	<0.001

¹Mean (SD)²Kruskal-Wallis rank sum test