Research Article

Pharmacological Management of HIV Infection and Hypertension and its Impact on Disease Control in Hypertensive People Living with HIV

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ABSTRACT

Hypertension has become a major comorbidity among people living with HIV (PLWH). However, studies examining drug use in hypertensive PLWH are scant. This study assessed the pharmacological management of HIV-hypertension in hypertensive PLWH as well as the effects of prescribed drugs on control of both diseases. The study utilized the case notes of 182 hypertensive PLWH recruited into a randomized controlled trial in the University of Uyo Teaching Hospital, Akwa Ibom State, Nigeria. Patient variables, including prescribed antiretroviral and antihypertensive drugs, were retrieved from the case notes between September and October 2019. Data were analyzed with SPSS (version 25.0). Patients were mostly females (59.3%), with a mean age of 50.2±8.8 years The antiretroviral regimen prescribed for most (77.5%) of the patients consisted of two nucleoside reverse transcriptase inhibitors (tenofovir, lamivudine) and an integrase inhibitor (dolutegravir). Hydrochlorothiazide (a diuretic), lisinopril (an angiotensin converting enzyme inhibitor) and amlodipine (a calcium channel blocker) comprised 79.1%, 74.7%, and 60.4% of prescribed antihypertensive drugs, respectively. The majority (95.1%) of patients had their antihypertensive drugs prescribed in combination. HIV infection and blood pressure (BP) were controlled in 74.7% and 39.6% patients, respectively. BP control was observed in 88.9% of patients prescribed monotherapy, and in 30.1% of patients on at least three antihypertensive drugs (p = 0.001). Pharmacological management of HIV-hypertension in this facility was appropriate. However, BP control was not achieved in majority of the cases studied despite the widespread use of combination antihypertensive drugs. An individualized approach to managing hypertension is recommended in hypertensive PLWH.

Keywords: Antiretroviral drugs; Antihypertensive drugs, Comorbidity, HIV, Hypertension; Prescription pattern.

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INTRODUCTION

The availability and use of effective combination antiretroviral therapy has considerably improved the quality of life as well as the survival of people living with HIV (PLWH). However, this has increasingly exposed this population to the risks of other non HIV-related comorbidities such as hypertension, dyslipidemia, and endocrine disorders.[1,2] Cardiovascular diseases have been implicated as one of the major causes of death with hypertension being the primary risk factor both in PLWH and in the general population.[3-5] Hence, appropriate treatment and control of hypertension as well as the viral (HIV) infection is crucial in hypertensive PLWH.

Managing HIV infection with hypertension in patients with both conditions may be challenging for patients (together with their caregivers) and health care providers, particularly in low- and middle-income countries with weak healthcare systems.[6] Pharmacological management requires careful drug selection to avoid clinically important drug interactions between antihypertensive and antiretroviral drugs.[7] Clinical failure of antiretroviral therapy and poor blood pressure control have both been attributed to such drug-drug interactions, which are often pharmacokinetic in character.[8-10] The interactions could also result in higher drug levels in the body due to inhibition of the enzymes involved in the metabolism of such drugs, thereby causing toxicity to the patient.

The major classes of antiretroviral drugs are the nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors, further classified as attachment inhibitors, fusion inhibitors, and chemokine receptor antagonists, integrase strand transfer inhibitors (INSTI), and pharmacokinetic enhancers/PI boosters. These different classes of antiretroviral drugs act at different points of the HIV life cycle. The use of combinations of a minimum of three drugs from at least two different classes is recommended in the management of HIV infection. Typically, a backbone of two NRTIs combined with an INSTI, a NNRTI or a PI is used.[8] Due to the increased risk of developing drug resistance, management with one or two antiretroviral medications is not recommended.[8] The recommendations are generally based on availability, accessibility, affordability, long term efficacy, barrier to resistance, safety, practice guidelines, and clinician preference.[11-13]

Similar to the general population, both non-pharmacological and pharmacological methods are employed in the management of hypertension in PLWH.[14,15] Essentially, the non-pharmacological approach involves lifestyle modifications. Pharmacotherapy is initiated when non-pharmacological approaches do not adequately control blood pressure, or in case of severe hypertension, evidence suggestive of target organ damage, renal disease, a high risk of or established cardiovascular disease, or diabetes mellitus.[16,17] However, concurrent non-pharmacological management is essential.[18] Antihypertensive drugs are represented by five major classes: angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), diuretics, calcium channel blockers (CCBs), and β-blockers. As in the general HIV-uninfected population, the class of antihypertensive medication prescribed is determined by the presence of specific complications of hypertension or comorbidities (compelling indications) e.g., chronic renal disease, heart failure, ischemic heart disease, diabetes, etc.[19]

In spite of the fact that hypertension has become a major comorbidity among PLWH, only a few studies have described the drug prescribing patterns in this comorbidity in health facilities.[5,20,21] Hence, the aim of this study was to describe the drug prescribing pattern in HIV and hypertension comorbidity in a tertiary hospital in Nigeria, and to evaluate its impact on disease control.

MATERIALS AND METHODS

This was a descriptive cross sectional study conducted in the HIV clinic of the 500-bed capacity University of Uyo Teaching Hospital, Uyo, Akwa Ibom State, Nigeria. The study utilized the case notes of participants recruited into a randomized controlled trial among hypertensive PLWH.[22] Participants were in the age range of 18 and 69 years, had been diagnosed of both HIV infection and hypertension, owned a personal phone, had been on antiretroviral and antihypertensive drugs for a minimum of three months, and gave informed consent to participate in the trial. Socio-demographic and clinical data of the participants, including antiretroviral and antihypertensive drugs they were placed on at the time, were retrieved from the medical records (case notes). The extracted information was documented in a data collection form. Data collection lasted for one month (September 16 – October 15, 2019).

Data were analyzed with SPSS (IBM version 25.0), and presented as mean (standard deviation) and frequency (percent). Chi square/Fisher's exact test was conducted to determine the association between blood pressure control and the number of antihypertensive drugs prescribed. Blood pressure control was defined as readings < 140/90 mmHg in line with the recommendations of the Eight Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) for hypertensive adults with diabetes or chronic kidney disease.[23] This is because hypertensive PLWH are predisposed to renal disease and metabolic abnormalities. Statistical significance for the analysis was set at $p < .05$.

Ethics approval for the study was obtained from the institutional Health Research Ethics Committee.

RESULTS

A total of 182 case notes were utilized for this study. The patients were mostly females (59.3%), with a mean age of 50.2 ± 8.8 years. Mean time since diagnosis of HIV infection and hypertension was 10.5 ± 4.2 years and 4.5 ± 4.1 years, respectively. Most of them were married (55.5%) and employed (58.8%) (Table 1).

Antiretroviral drugs

As shown in Table 2, majority (80.8%) of the participants were prescribed antiretroviral drugs consisting of two NRTIs and an INSTI. Specifically, tenofovir-lamivudine-dolutegravir combination was the most frequently prescribed (n = 141, 77.5%). Only 12 (6.6%) were prescribed a combination of two NRTIs and a ritonavir-boosted PI.

Antihypertensive drugs

Diuretics (88.5%), ACEIs (75.8%) and CCBs (63.2%) were the most frequently prescribed classes of drugs for hypertension in the study population. Specifically, hydrochlorothiazide (a thiazide diuretic), lisinopril (an ACEI) and amlodipine (a CCB) accounted for 79.1%, 74.7% and 60.4% of the prescribed antihypertensive drugs, respectively. A combination of at least 3 classes of antihypertensive drugs was the most common regimen (51.1%). Only nine (4.9%) of the participants were on monotherapy (Table 3).

Control of HIV infection and blood pressure

Table 1 shows that 136 (74.7%) of the participants had virological control (i.e. viral load < 40 cells/ml). However, only 72 (39.6%) had controlled (< 140/90 mmHg) blood pressure.

Figure 1 shows the distribution of blood pressure control by the number of antihypertensive drugs prescribed. Results of Fisher's Exact test indicate a statistically significant association between blood pressure control and the number of antihypertensive drugs prescribed: $\chi^2 = 13.339$, $p = 0.001$. Most (88.9%) of the patients prescribed monotherapy had their blood pressure under control. However, majority (69.9%) of the patients prescribed a combination of at least three antihypertensive drugs did not achieve blood pressure control (Table 4).

Table 1: Socio-demographic and clinical data of participants (N = 182)

Variable	Mean	SD
Age (years)	50.2	8.8
Duration since HIV infection diagnosis (years)	10.5	4.2
Duration since hypertension diagnosis (years)	4.5	4.1
	n	**%**
Gender		
Male	74	40.7
Female	108	59.3
Education		
None	4	2.2
Primary	52	28.6
Secondary	71	39.0
Tertiary	55	30.2
Marital status		
Single	17	9.3
Married	101	55.5
Widowed	54	29.7
Divorced	10	5.5
Employment Status		
Working	107	58.8
Not working	53	29.1
Retired	22	12.1
Virological control		
Yes (VL <40 copies/ml)	136	74.7
No (VL ≥40 copies/ml)	46	25.3
Blood pressure control		
Yes (<140/90 mmHg)	72	39.6
No (≥140/90 mmHg)	110	60.4

Note. SD Standard deviation; *VL* Viral load.

Table 2 Antiretroviral treatment regimen (N = 182)

Antiretroviral drug regimen	Frequency	Percent
2NRTIs + INSTI	**147**	**80.8**
Tenofovir[1] + Lamivudine + Dolutegravir	141	77.5
Abacavir + Lamivudine + Dolutegravir	6	3.3
2NRTIs + NNRTI	**23**	**12.6**
Tenofovir[1] + Lamivudine + Efavirenz	7	3.8
Abacavir + Lamivudine + Efavirenz	12	6.6
Zidovudine + Lamivudine + Efavirenz	4	2.2
2NRTIs + PI/r	**12**	**6.6**
Abacavir + Lamivudine + Atazanavir/r	6	3.3
Abacavir + Lamivudine + Lopinavir/r	4	2.2
Tenofovir[1] + Lamivudine + Atazanavir/r	2	1.1

Note: [1]Tenofovir disoproxil fumarate; *NRTI* Nucleoside/ Nucleotide reverse transcriptase inhibitor; *NNRTI* Non-nucleoside reverse transcriptase inhibitor; *INSTI* Integrase strand transfer inhibitor; *PI/r* Ritonavir-boosted protease inhibitor.

Table 3: Antihypertensive drug prescription pattern (N = 182)

Antihypertensive drug	Frequency	Percent
Angiotensin converting enzyme inhibitors	**138**	**75.8**
Lisinopril	136	74.7
Ramipril	2	1.1
Angiotensin II receptor antagonists	**18**	**9.9**
Losartan	5	2.7
Telmisartan	13	7.1
Calcium channel blockers	**115**	**63.2**
Amlodipine	110	60.4
Nifedipine	5	2.7
Central alpha-2 agonist	**17**	**9.3**
Methyldopa	17	9.3
Beta-blocker	**3**	**1.6**
Atenolol	3	1.6
Diuretics	**161**	**88.5**
Hydrochlorothiazide	144	79.1
Indapamide	1	0.5
Amiloride hydrochloride+ Hydrochlorothiazide	16	8.8
Antihypertensive Regimen		
Monotherapy	9	4.9
Combination of 2 drugs	80	44.0
Combination of ≥3 drugs	93	51.1

Table 4 Association between blood pressure control and the number of antihypertensive drugs prescribed

Number of drugs	Blood Pressure Control		χ^2	*P*
	Controlled	Not controlled		
One	8 (88.9%)	1 (11.1%)	13.339	**0.001**
Two	36 (45.0%)	44 (55.0%)		
Three or more	28 (30.1%)	65 (69.9%)		
Total	***72 (39.6%)***	***110 (60.4%)***		

Note. Bold value indicates statistical significance at $p < 0.05$

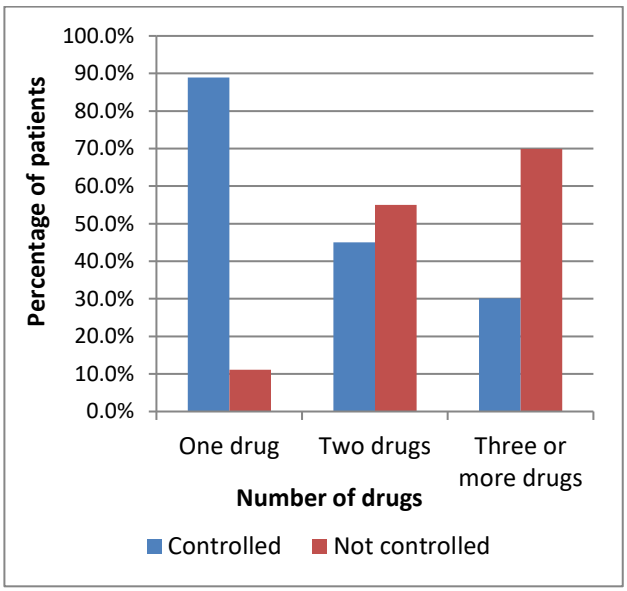

Figure 1: Distribution of blood pressure control by the number of antihypertensive drugs prescribed

DISCUSSION

This study examines the prescription pattern in HIV-hypertension comorbidity and its impact on control of both diseases at a Nigerian hospital. We found that a clear majority of the study participants were prescribed an antiretroviral regimen consisting of two NRTIs and an INSTI i.e. tenofovir disoproxil fumarate, lamivudine and dolutegravir. The three most frequently prescribed medications for hypertension were hydrochlorothiazide (a diuretic), lisinopril (an ACEI), and amlodipine (a CCB); majority were taking at least three antihypertensive drugs. While virological control was observed in most of the cases studied, blood pressure control was not achieved in majority of the cases despite the widespread use of combination antihypertensive drugs.

The prescription of a combination of tenofovir, lamivudine and dolutegravir is in accordance with the National guideline for HIV prevention, treatment and care as well as the World Health Organization which recommends the use of two NRTI and an INSTI or NNRTI as the preferred first line regimen for management of HIV infection in adults and adolescents.[8,24] This regimen usually comes in single-pill combination, to be taken once daily. We observed a significant control of HIV infection among the participants as majority had undetectable plasma viral loads (i.e. viral load < 40 cell/ml). Nevertheless, this is still less than the third '95' of the 95-95-95 target for ending the AIDS epidemic by 2030. This target aims for a suppressed or undetectable viral load in 95% of PLWH receiving antiretroviral therapy, ensuring that their immune systems are strong and that they are no longer infectious.[25]

Diuretics, ACEIs and CCBs were the three classes of drugs for hypertension that were most frequently prescribed in the present study. This contradicts the findings of a previous study which reported β-blockers and CCBs as the most frequently prescribed antihypertensive drug classes.[20] De Socio et al.[21] and Manner et al.[5] reported the prescription of ACEIs/ARBs in about three-quarters of their study population. Our results are in line with generally recognized guidelines.[11,14,17] For instance, the World Health Organization recommends using any one or a combination of medications from the three classes – ACEIs/ARBs, long-acting dihydropyridine CCBs, and thiazide (and thiazide-like) diuretics – as an initial course of treatment.[17] Of the dihydropyridine CCBs, amlodipine is preferred because it has a lower first-pass effect and a higher oral bioavailability, which make it less prone to interact with other drugs.[7] Similarly, IAPAC protocols for the integrated management of HIV and noncommunicable disease recommends hydrochlorothiazide (a diuretic) as the preferred initial antihypertensive medication in hypertensive PLWH; enalapril (an ACEI) should be added if blood pressure is not at target even after titrating to a maximum dose (25mg).[14] However, as there are no interactions between these two antihypertensives and antiretroviral medications, IAPAC advises that this combination be taken at the same time as the antiretroviral medications, possibly to increase adherence and persistence.[14] Further, the European AIDS Clinical Society guidelines recommend an initial dual regimen of an ACEI or ARB combined with a CCB or a thiazide-type diuretic, or for black persons, an initial dual combination of a CCB and a thiazide-type diuretic.[11] If blood pressure is not controlled with the initial therapy, a triple regimen of ACEI or ARB, a CCB and a thiazide-type diuretic is recommended.[11]

Plasma concentration of CCBs may be increased in the presence of PIs and reduced in the presence of NNRTIs.[14] To avoid such interactions, hypertensive PLWH may require dosage adjustment of the CCB or alteration of timing of administration, and monitoring with electrocardiograms.[11,14] In the setting where the present study was conducted, patients are usually advised to take both classes of drugs (antiretroviral and antihypertensive) at least 6 hours apart to avoid potential drug-drug interactions.

The current study found that a clear majority of the study population were prescribed more than one antihypertensive drug. This is in contrast to previous studies which indicated that the majority of hypertensive

PLWH were prescribed monotherapy of antihypertensive drugs.[5,21] According to JNC8, many people with hypertension will require more than one antihypertensive drug to achieve blood pressure control.[23] Additionally, blood pressure control is likely to be achieved sooner with combination therapy.[17] Nevertheless, for the majority of the patients in this study, this did not lead to adequate blood pressure control. Majority of the patients prescribed monotherapy of antihypertensive drugs had their blood pressure under control; on the other hand, majority of those taking at least a combination of three different antihypertensive drugs did not achieve blood pressure control. This finding may be related to the total number of drugs to be taken daily, or the 'pill burden'. A high pill burden is a known barrier to medication adherence. To improve medication adherence/persistence and blood pressure control, guidelines from the European AIDS Clinical Society and the World Health Organization both advocate single-pill combination therapy whenever possible.[11,24] In this study, the antihypertensive drug combinations were typically prescribed and taken singly. However, it should be noted that because this was a cross-sectional study, causality could not be established. That is, whether blood pressure control status was influenced by the number of antihypertensive drugs prescribed or vice versa.

The suboptimal control of blood pressure in a significant number of the cases studied corroborates earlier findings of studies conducted in other settings.[5,21,26] This is in spite of the fact that PLWH (including hypertensive PLWH) have regular and routine access to healthcare. This global trend is worrisome and needs the utmost attention. It is critical that variables causing inadequate blood pressure control (relative to virological control) in this patient population be assessed and addressed on a regular basis.

Limitations

Limitations of this study should be noted. Although the study was conducted as part of a prospective longitudinal study, the results indicate the prescription pattern at the end of the study. We did not compare the prescription pattern at different points over the course of the study. Furthermore, the interventions of the pharmacist reported in the publication of the clinical outcomes of the randomized controlled trial[22] had a positive impact on blood pressure control in the present study. In spite of this, the finding of suboptimal control of blood pressure relative to HIV infection in the present study is consistent with earlier findings in hypertensive PLWH. Furthermore, because just one hospital was used for the study, there is limited generalizability of the findings. Lastly, since the study utilized the participants' medical records (case notes), only information that was recorded could be retrieved; information about any prescription changes, for instance, that were not documented, would have been missed.

CONCLUSION

The results of this study showed that the medications prescribed for the management of HIV and hypertension in hypertensive PLWH were in compliance with standard treatment guidelines. Although combination antihypertensives were prescribed to the majority of the patients, blood pressure control was less than optimal. Hence, there is a need for an individualized approach to the therapy of hypertension as well as periodic evaluation of potential factors influencing the control of the disease in hypertensive PLWH.

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