

Prevalence, Awareness, and Factors Associated with Hypertension Among People Living with HIV in Eastern Uganda. A Multicentre Cross-Sectional Study

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Introduction: Despite advancements in Antiretroviral Therapy (ART), people living with HIV (PLHIV) face increasing risks of HTN, leading to significant morbidity and premature mortality, undermining the hard-earned gains of fighting HIV. The prevalence of hypertension among HIV patients and associated risk factors has not been extensively studied in the rural parts of Uganda.

Objective: We assessed the prevalence, awareness, and factors associated with hypertension among PLHIV at two health facilities in Eastern Uganda.

Methods: A cross-sectional study was conducted at Mbale Regional Referral Hospital and Bugobero Health Center IV HIV clinics from May to July 2023. We recruited patients with HIV above the age of 18 years and willing to consent. Participants were interviewed using a structured questionnaire adapted from the WHO STEPwise approach to noncommunicable disease risk factor surveillance (STEPS) and the AIDS Clinical Trials Group. Anthropometric measurements and blood pressure were taken. Bivariate and multi-variable logistic regression were performed. A P value <0.2 in the bivariate analysis was transferred to the multivariable logistic regression model. A P value <0.05 was statistically significant.

Results: The study surveyed 400 PLHIV with a mean age of 46.5 (SD: 12.4) years; most were female ($n=261$, 65.3%). Hypertension prevalence was at 37.5%, with 20.5% in stage 2 and 68% ($n=102$) of hypertensive participants were unaware. Hypertension was associated with age ≥ 50 years (aOR: 2.11, 95% CI: 1.33–3.37, $p = 0.002$), a suppressed viral load (aOR: 3.71, 95% CI: 1.02–5.13, $p = 0.046$) and BMI ≥ 25 Kg/m² (aOR: 1.64, 95% CI: 1.01–2.66, $p = 0.044$).

Conclusion: Hypertension is a significant burden among PLHIV in Eastern Uganda, influenced by HIV and lifestyle-related risk factors. Improved screening and diagnosis are needed with close monitoring for patients with viral load suppression due to the possible negative effects of ART on blood pressure.

Plain Language Summary: This study explored the prevalence, awareness, and risk factors linked to high blood pressure among people living with HIV (PLHIV) at two health facilities in Eastern Uganda. We found that 37.5% of the participants had high blood pressure, yet the majority (68%) were unaware of their condition. We identified older age ≥ 50 years, a higher body mass index (BMI) ≥ 25 kg/m², and having a suppressed viral load as significant risk factors for high blood pressure among PLHIV. These results reveal the urgent need for improved health strategies that integrate the management of HIV and hypertension and preventive care to enhance the overall health outcomes for PLHIV in rural areas.

Keywords: human immunodeficiency syndrome, antiretroviral therapy, hypertension, body mass index

Introduction

Sub-Saharan Africa (SSA) continues to face a significant burden of HIV/AIDs, with about 20.8 million People Living with HIV (PLHIV) and approximately 450,000 new infections in 2023.¹ As the lifespan of PLHIV increases due to the availability of Antiretroviral Therapy (ART),² there is a notable rise in cardiovascular disease-related mortality among them,^{3,4} with hypertension (HTN) being the leading risk factor.^{5,6} PLHIV and HTN have a significantly increased risk of mortality compared to non-HIV-infected people with HTN.⁷ As of 2022, Uganda had a 5.5% HIV prevalence rate, with 54,000 new infections annually amidst a high prevalence of hypertension (26.4%), with an increasing trend over the past ten years.^{8–10}

Several factors have been implicated in the increasing prevalence of HTN among PLHIV. Certain types of ARTs, like atazanavir, stavudine, and raltegravir, have been associated with metabolic complications, such as lipodystrophy, dyslipidemia, lactic acidosis, and glucose intolerance that herald HTN.^{2,11} Lifestyle-related risk factors like poor dietary habits, physical inactivity, and obesity have also been implicated as predictors of HTN among PLHIV.^{12–14} Furthermore, there is a correlation between the aging population of PLHIV with multiple comorbidities and their increased susceptibility to HTN.¹⁵ Collectively, the factors are multifaceted, encompassing HIV-related ART treatments and alterations in lifestyle.^{16,17}

The hypertension HIV comorbidity is worsening health outcomes among PLHIV, threatening the gains achieved over the years.¹⁸ Studies in Uganda have revealed a relatively high burden of hypertension among PLHIV, ranging from 20.9% to 29%.^{12,19,20} However, these have predominantly focused on large HIV clinics in urban areas of central Uganda, with a few representing rural regions in the East and Southwest.^{21,22} In addition, only 7.7% of Ugandans with hypertension were aware of their high blood pressure in a national survey.⁸ It is imperative to understand the drivers of hypertension among PLHIV and their levels of awareness of the diseases in varied settings, factoring in differences in socio-cultural and lifestyle contexts in Uganda.

This study determined the prevalence, awareness, and factors associated with hypertension among PLHIV at two HIV clinics of health facilities at different levels, both in a rural and urban setting in Eastern Uganda. This endeavor seeks to offer a comprehensive understanding of the prevalence of the most common cardiovascular disease among PLHIV, considering both HIV-related and other modifiable risk factors to guide the development of multifaceted prevention and management strategies to address this dual burden.

Methods

Study Design

This was a quantitative cross-sectional study using a structured questionnaire carried out between May and July 2023.

Study Site and Settings

This study was conducted at two health facilities: Mbale Regional Referral Hospital (MRRH) and Bugobero Health Center (HC) IV HIV clinics in Eastern Uganda. These are large public health facilities providing HIV care within the greater Mbale region where the study was conducted. MRRH is a 455-bed capacity hospital, the main referral for the Eastern region with a catchment area of 4 million people, and the HIV clinic sees approximately 300 patients per month. The Bugobero HC IV HIV clinic serves approximately 60 patients per month.

Study Participants

We included PLHIV on ART receiving HIV care within the study facilities during the study period who were ≥ 18 years of age, more than six months on ART, and willing to consent. We excluded HIV patients in poor clinical condition (advanced HIV disease) at the time of study and those who were not willing to consent.

Sample Size

The sample size was calculated using the formula $=Z^2P(1-P)/d^2$. We considered the standard deviation at 1.960, the precision of the estimate of 5%, and the prevalence value of HTN among PLHIV at 46.9% from a study by Muddu et al in Eastern Uganda.²² The calculated sample size was 382.68. To cater for non-respondents, 10% of the sample size was added to get a final sample size of 421 participants.

Sampling Procedure

Eligible participants were recruited using a convenience sampling method from patients attending scheduled appointments on three specific days of the week: Monday, Tuesday, and Thursday. Within this convenience sample, participants were randomly selected by choosing their files from those present on these days. After being identified, participants were asked to participate in the study, and written informed consent was obtained.

Data Collection Tool and Procedure

The questionnaire was developed and modified from the structured questionnaire used by the WHO STEPwise approach to noncommunicable disease risk factor surveillance (STEPS).⁸ An additional section on the history of ART use was adopted from a validated questionnaire developed by the AIDS Clinical Trials Group (ACTG).²³ The questionnaire collected sociodemographic data such as age, sex, education level, residence, and occupation; lifestyle factors like tobacco use, alcohol consumption, fruit servings, and physical activity; clinical parameters such as time since HIV diagnosis, time since ART was initiated, type of ART, previous history of HTN, family history of HTN, and viral load.

A trained research assistant administered a questionnaire in English or the local dialect, depending on the participant's convenience, conducted anthropometric measurements, and measured blood pressure. Weight was measured using a calibrated weighing scale in kilograms (Kgs), and height was measured using a stadiometer in centimetres, then converted to meters (m). Blood pressure was measured using a well-calibrated digital blood pressure machine twice with a resting time interval of 5 minutes and an average taken. Patients identified with high blood pressure and unaware were notified to the ART clinic team for further evaluation and appropriate management.

Measurement Definitions

Body mass index (BMI) was computed from weight and height as kg/m^2 . BMI was categorized as underweight (18.5 kg/m^2), normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), and Obese ($\geq 30 \text{ kg/m}^2$). Hypertension was defined as systolic blood pressure (SBP) $>140 \text{ mmHg}$ and/or diastolic blood (DBP) pressure $>90 \text{ mmHg}$ or a prior diagnosis from the clinic. It was further categorized into stage 1 hypertension (SBP 140 – 159 mmHg or DBP 90 – 99 mmHg) and stage 2 hypertension (SBP $\geq 160 \text{ mmHg}$ or DBP $\geq 100 \text{ mmHg}$).

Study Outcome

The primary outcome was having hypertension and prior awareness of the diagnosis.

Data Analysis

Fully completed questionnaires were entered into a Kobo toolbox form, extracted into Microsoft Excel 2016 computer software, coded, and analyzed using STATA 15.0. The characteristics of the participants were summarized as frequencies and proportions and are presented in tables and charts. Exposure variables were compared against hypertension using the chi-square or Fischer's exact test. Independent *t*-test was performed to compare gender differences in blood pressure. Univariable and multivariable logistic regression analyses were performed to determine factors independently associated with hypertension, reporting adjusted odds ratios (aORs) and 95% confidence intervals (CIs). Any exposure variable with a *p*-value of 0.2 at univariable analysis was transferred to the multivariable logistic regression model. A two-sided *P* value of less than 0.05 was regarded as statistically significant.

Results

Characteristics of the Participants

We surveyed 400 participants, with a mean age of 46.5 (SD: 12.4) years. Most were female ($n=261$, 65.3%) and had attained primary-level education ($n=207$, 51.8%). More than half lived in a rural area ($n=229$, 57.2%), and almost half were unemployed ($n=171$, 42.7%).

Regarding lifestyle and behavioural characteristics, about 38 (9.5%) participants were underweight. The majority ($n=234$, 58.5%) were in the normal BMI range, and 128 (32%) had a BMI ≥ 25 (overweight or obese). A relatively higher

proportion of the participants had a history of alcohol intake (55.3%), and the proportion of people who smoke cigarettes was low (13.0%).

Clinically, viral load was suppressed in almost all participants (n=379, 94.7%). The majority (n=351, 87.7%) of participants had been on ART for over five years, and 122 (30.5%) had lived with HIV for ≥ 15 years. The most prescribed regimen was Tenofovir, Lamivudine, and dolutegravir (TLD) (n=369, 92.2%). [Table 1](#).

Table 1 Socio-Demographic Characteristics of Participants (N=400)

Variable	Freq (%)	Hypertensive		p-Value
		Yes (%)	No (%)	
Overall	400 (100)	150 (37.5)	250 (62.5)	
Age Mean ± SD	46.5 ± 12.4			
Age Category				
18–24	29 (7.3)	0 (0)	29 (11.6)	<0.001
25–49	206 (51.5)	66 (44.0)	140 (56.0)	
50 Above	165 (41.2)	84 (56.0)	81 (32.4)	
Sex				
Female	261 (65.2)	97 (64.7)	164 (65.6)	0.849
Male	139 (34.8)	53 (35.3)	86 (34.4)	
Residence				
Rural	229 (57.2)	81 (54.0)	148 (59.2)	0.309
Urban	171 (42.3)	69 (46.0)	102 (40.8)	
Education Level				
Primary	207 (51.7)	70 (46.7)	137 (54.8)	0.053
Secondary	117 (29.3)	41 (27.3)	76 (30.4)	
Tertiary	43 (10.8)	22 (14.7)	21 (8.4)	
None	33 (8.2)	17 (11.3)	16 (6.4)	
Employment Status				
Informal	171 (42.7)	63 (42.0)	108 (43.2)	0.804
Unemployed	171 (42.7)	63 (42.0)	108 (43.2)	
Formal	58 (14.6)	24 (16.0)	34 (13.6)	
Years with HIV				
10–14	135 (33.7)	48 (32.0)	87 (34.8)	0.032
15 or more	122 (30.5)	57 (38.0)	65 (26.0)	
5–9	96 (24.0)	34 (22.7)	62 (24.8)	
0–4	47 (11.8)	11 (7.3)	36 (14.4)	

(Continued)

Table 1 (Continued).

Variable	Freq (%)	Hypertensive		p-Value
		Yes (%)	No (%)	
Viral Load Status				
Suppressed	379 (94.7)	147 (98.0)	232 (92.8)	0.024
Non suppressed	21 (5.3)	3 (2.0)	18 (7.2)	
Years on ART (Months)				
61 and above	351 (87.7)	139 (92.7)	212 (84.8)	0.081
13–60	34 (8.5)	8 (5.3)	12 (4.8)	
6–12	15 (3.8)	3 (2.0)	26 (10.4)	
Current Regimen				
TLD	369 (92.2)	133 (88.7)	236 (94.4)	0.036
ART with Protease Inhibitor	15 (3.7)	11 (7.3)	4 (1.6)	
TLE	5 (1.3)	2 (1.3)	3 (1.2)	
Others	11 (2.8)	4 (2.7)	7 (2.8)	
Smoking				
Yes	52 (13.0)	20 (13.3)	32 (12.8)	0.878
No	349 (87.0)	130 (86.7)	218 (87.2)	
Alcohol				
Yes	221 (55.3)	93 (62.0)	127 (50.8)	0.021
No	179 (44.7)	57 (38.0)	123 (49.2)	
Physical Activity				
Moderate	221 (55.3)	88 (58.7)	133 (53.2)	0.767
Vigorous	162 (40.5)	56 (37.3)	106 (42.4)	
None	14 (3.5)	5 (3.3)	9 (3.6)	
Light	3 (0.7)	1 (0.7)	2 (0.8)	
BMI Mean ± SD	23.4 ± 4.3			
Normal	234 (58.5)	82 (54.7)	152 (60.8)	< 0.001
Overweight	93 (23.2)	42 (28.0)	51 (20.4)	
Underweight	38 (9.5)	5 (3.3)	33 (13.2)	
Obese	35 (8.8)	21 (14.0)	14 (5.6)	
Hypertension Family history				
Yes	159 (39.7)	71 (47.3)	88 (35.2)	0.016
No	241 (60.3)	79 (52.6)	162 (64.8)	

Note: Bolded values are statistically significant at $P < 0.05$. ART: Antiretroviral Therapy, TLD: Tenofovir, Lamivudine, and Dolutegravir, TLE: Tenofovir lamivudine efavirenz, BMI: Body Mass Index.

Abbreviations: ART, Antiretroviral Therapy; TLD, Tenofovir Lamivudine and Dolutegravir; TLE, Tenofovir lamivudine efavirenz; BMI, Body Mass Index.

Prevalence and Awareness of Hypertension

Hypertension was observed in 37.5% ($n=150$) of the study population. Most hypertensive participants (68%, $n=102$) were unaware of their condition (Figure 1). The highest recorded SBP was 222 mmHg, and the lowest was 97 mmHg, with a mean of 138.1 ± 21.9 mmHg. For DBP, the highest recorded was 145 mmHg, and the lowest was 61 mmHg, with a mean of 87.9 ± 15.4 mmHg. There was no significant difference between the mean SBP of female and male participants (Female: 137.5 vs Male: 139.1 mmHg, $p=0.493$) and DBP (Female: 88.1 vs Male: 87.8 mmHg, $p=0.854$) (Figure 2). Stage 1 and 2 HTN represented 13.3% and 20.5% of the participants, respectively. Stage 2 hypertension was most prevalent (59.8%) among individuals over 50 years of age (Figure 3).

The prevalence of hypertension increased with age (25–49 years: 44.0%; ≥ 50 years: 56.0%, $p<0.001$) and was higher among individuals who had been living with HIV for 15 years or more (38.0%, $p=0.032$), had viral load suppression (98%, $p=0.024$), consumed alcohol (62.9%, $p=0.021$), and did not have a family history of hypertension (52.6%, $p=0.016$). Although individuals on protease inhibitor-based ART regimens constituted only 3.7% ($n=15$) of the participants, they had a high prevalence of hypertension (7.3%, $n=11$) (Table 1).

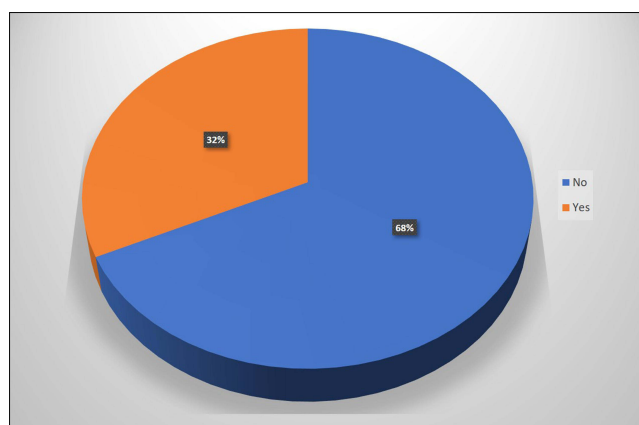


Figure 1 Percentage awareness of hypertension among hypertensive patients with HIV ($N=150$).

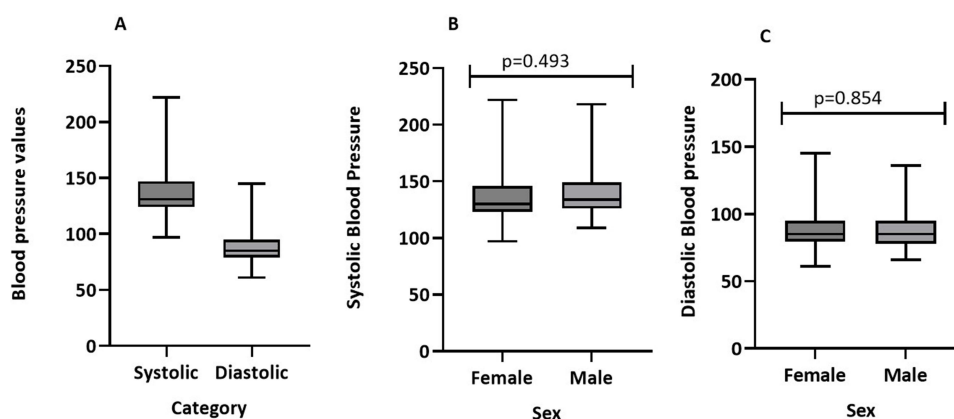


Figure 2 Distribution of Systolic and Diastolic Blood Pressure Values (A). Comparison by sex of SBP (B) and DBP values (C). No significant difference was observed between the sexes. An Independent *t*-test was performed.

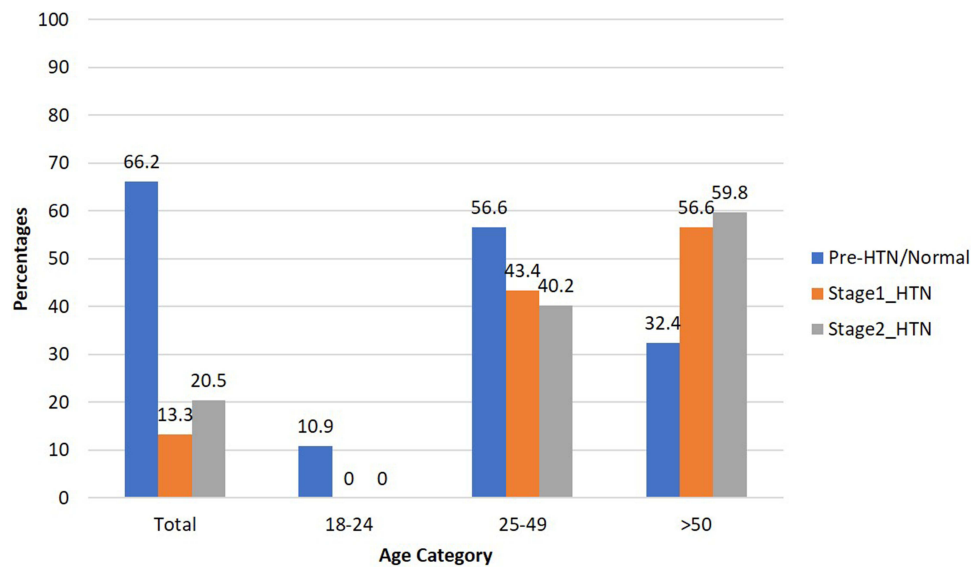


Figure 3 Categorization of hypertension according to stages and Age.

Factors Associated with Hypertension

Age, viral load status, and BMI were independently associated with hypertension. Individuals aged ≥ 50 were more than twice as likely to have hypertension compared to those aged 25–49 (Adjusted odds ratio (aOR): 2.11, 95% CI: 1.33–3.37, $p=0.002$). Patients with a suppressed viral load were 3.71 times more likely to have hypertension than those with a non-suppressed viral load (aOR: 3.71, 95% CI: 1.02–5.13, $p=0.046$). Furthermore, a BMI of ≥ 25 kg/m² was associated with 64% higher odds of hypertension than a BMI below 25 (aOR: 1.64, 95% CI: 1.01–2.66, $p=0.044$). [Table 2](#).

Table 2 Factors Associated with Hypertension Among People Living with HIV in Eastern Uganda

Variable	cOR (95% CI)	p-Value	aOR (95% CI)	p-Value
Age Category				
25–49	Ref		Ref	
50 Above	2.19 (1.44–3.36)	<0.001	2.11 (1.33–3.37)	0.002
18–24	I		I	
Sex				
Female	Ref			
Male	1.04 (0.68–1.59)	0.849		
Residence				
Rural	Ref			
Urban	1.24 (0.82–1.86)	0.309		
Education Level				
None/Primary	Ref			
Secondary/Tertiary	1.14 (0.76–1.72)	0.527		

(Continued)

Table 2 (Continued).

Variable	cOR (95% CI)	p-Value	aOR (95% CI)	p-Value
Employment Status				
Unemployed	Ref			
Employed	1.05 (0.70–1.58)	0.814		
Years with HIV				
<10 years	Ref		Ref	
>10 years	1.50 (0.98–2.32)	0.064	1.24 (0.77–2.01)	0.364
Viral Load Status				
Non-suppressed	Ref		Ref	
Suppressed	3.80 (1.10–7.32)	0.035	3.71 (1.02–5.13)	0.046
Years on ART (Months)				
6–12	Ref			
13–60	1.13 (0.25–5.06)	0.875		
61 and above	2.40 (0.66–8.77)	0.184		
Current Regimen				
Others	Ref		Ref	
TLD	0.99 (0.28–3.43)	0.983	1.07 (0.30–3.86)	0.908
Protease Inhibitors	4.81 (0.89–2.57)	0.067	5.98 (0.92–8.90)	0.062
TLE	1.17 (0.13–1.22)	0.889	1.10 (0.12–9.14)	0.930
Smoking				
No	Ref			
Yes	1.04 (0.57–1.91)	0.878		
Alcohol				
No	Ref		Ref	
Yes	1.63 (1.07–2.46)	0.021	1.48 (0.93–2.37)	0.120
Physical Activity				
None/Light	Ref		Ref	
Moderate/Vigorous	1.10 (0.39–3.05)	0.848	1.78 (0.53–5.91)	0.357
BMI				
< 25	Ref		Ref	
≥ 25	2.06 (1.34–3.17)	0.001	1.64 (1.01–2.66)	0.044
Hypertension Family history				
No	Ref		Ref	
Yes	1.65 (1.09–2.49)	0.017	1.55 (0.98–2.45)	0.060

Notes: Bolded values are statistically significant at $P < 0.05$.

Discussion

This study revealed a notably high prevalence of hypertension (37.5%) among PLHIV, with almost a quarter (20.5%) in stage 2 hypertension. This finding is reinforced by a retrospective study in the same Eastern region that enrolled a larger number of 1649 participants and reported a higher prevalence of HTN (46.9%) among PLHIV.²² Other studies in the central region of Uganda reported comparatively lower but still high prevalences ranging from 20.9% to 29%.^{12,19,20} The geographical differences in prevalences are concordant with the results of the most recent national survey that reported the highest prevalence of hypertension in the Eastern region (37.3%) compared to the Western (36.1%), central (32.0%) and Northern (21.7%) Uganda.²⁴ Furthermore, another study at an HIV clinic in central Uganda revealed a gradual rise in the prevalence of hypertension among PLHIV, from 16.9% in 2009 to 32.3% in 2013.²⁵ Together, the studies indicate an upward trend in hypertension prevalence in Uganda over the years that needs urgent attention.

Unfortunately, the study reveals that more than half of the hypertensive participants (68%) were unaware of their status. This could be attributed to the population's ignorance of the disease, as we discovered that more than half (55.0%) of the participants had not measured their blood pressure in the past year. Similarly, about 70% of PLHIV in a study from central Uganda were unaware of their hypertensive status.²⁶ This reflects statistics of the general population in Uganda, where 82.3% of those with hypertension were not aware of their raised blood pressure from a recent national survey in 2014.⁸ In addition, we found a significant proportion (20.5%) to have stage 2 hypertension, showing the concerning status of their uncontrolled hypertension. This is particularly concerning as poorly controlled hypertension is a leading cause of mortality among PLHIV.²⁷

This study revealed that hypertension was associated with increasing age, ≥ 50 years, and overweight/obesity among PLHIV, similar to several other studies done in LMICs.^{12–14,19,25} These risk factors have well-established associations with hypertension and cardiovascular disease. Shifts in lifestyle patterns and dietary habits could contribute to the observed association between hypertension and obesity. In addition, this study showed that PLHIV with suppressed viral loads were more likely to have hypertension, which is consistent with results from a study in Zambia.²⁸ However, this is contrary to literature that has associated higher viral load with a higher risk of hypertension among PLHIV, indicating a direct relationship between viral load and incident hypertension.^{27,29,30} Studies demonstrating a direct relationship between viral load and hypertension have used cumulative viral load measures rather than single-time point values, indicating that the former could be a more practical approach.³¹ In addition, ART could be implicated; while crucial for suppressing viral load and managing HIV, it can have side effects. Specific ART regimens like protease inhibitors have been shown to contribute to developing lipodystrophy and hyperlipidemias, which are associated with inflammation and damage to the vasculature.³² In the face of aging, these synergistically contribute to the development of hypertension.²⁸ Given the potential side effects of ART, particularly among patients with good adherence and suppressed viral loads, it is crucial to implement close monitoring of blood pressure and other cardiovascular risk factors in this population.

Strengths and Limitations

The strength of this study draws from its comprehensive evaluation of both HIV-related and lifestyle risk factors for HTN, which provides a broader understanding of the need for integrated preventive healthcare approaches in promoting cardiovascular health among PLHIV. The multicenter nature of facilities at different levels and urban and rural settings gives a varied picture. As such, although it included a moderate number of participants, it represents a relatively generalizable population of PLHIV in Eastern Uganda. The study also has some limitations. Data on lifestyle risk factors like smoking, alcohol, and marijuana usage, as well as physical activity, are self-reported and thus susceptible to social desirability bias.

Conclusion

The study reveals a high prevalence of hypertension among PLHIV in Eastern Uganda, with nearly a quarter already in stage 2 hypertension. Significantly, a substantial portion of hypertensive PLHIV remains unaware of their condition. The findings align with a concerning trend observed across Uganda, emphasizing the urgent need for targeted interventions. Age, overweight/obesity, and suppressed viral load emerged as key risk factors for hypertension. The association between viral load suppression and hypertension sheds light on the complex relationship between HIV infection, ART, and

cardiovascular health. It unveils the significance of closely monitoring hypertension in patients who adhere well to ART and achieve viral load suppression. Integrated preventive healthcare strategies, addressing both HIV-related and lifestyle risk factors, are imperative to curb the escalating burden of hypertension among PLHIV.

Abbreviations

ART, Antiretroviral Therapy; PLHIV, People Living with HIV; CVD, Cardiovascular Disease; WHO, World Health Organisation; ACTG, AIDS Clinical Trials Group; HTN, Hypertension; HC, Health Centre; BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

Ethics Approval and Informed Consent

The study was approved by the Busitema University Faculty of Health Sciences Research Ethics Committee (BUFHS-REC) under approval number BUFHS-2022-42. Additional permission was obtained from the administration of the study facilities. All participants were enrolled in the study after informed written consent was obtained. They were informed that participation was voluntary and that they could withdraw anytime. The ethical principles of involvement of human research subjects, as outlined in the Declaration of Helsinki, were adhered to.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Acknowledgments

The authors wish to thank the research assistants who collected data and the patients who accepted to participate in the study.

Author Contributions

All authors made a significant contribution to the article in its conceptualization, study design, execution, acquisition of data, analysis, and interpretation; took part in drafting, revising, and critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Royal Society of Tropical Medicine and Hygiene's early career researcher grant through the National Institute for Health and Care Research.

Disclosure

The authors report no conflicts of interest in this work.

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