ORIGINAL RESEARCH

Prevalence of and Factors Associated with Hypertension Among Adults on Dolutegravir-Based Antiretroviral Therapy in Uganda: A Cross Sectional Study

Ronald Kasoma Mutebi [1–3], Andrew Weil Semulimi [1,4], John Mukisa [5], Martha Namusobya [1], Joy Christine Namirembe [3], Esther Alice Nalugga [1], Charles Batte [1], David Mukunya [6], Bruce Kirenga [1,7], Robert Kalyesubula [4], Pauline Byakika-Kibwika [7]

[1]Lung Institute, Department of Medicine, School of Medicine, College of Health Sciences, Makerere University, Kampala, Uganda; [2]Clinical Epidemiology Unit, School of Medicine, College of Health Sciences, Makerere University, Kampala, Uganda; [3]Department of Medicine, Mengo Hospital, Kampala, Uganda; [4]Department of Physiology, School of Biomedical Sciences, College of Health Sciences, Makerere University, Kampala, Uganda; [5]Department of Immunology and Molecular Biology, School of Biomedical Sciences, College of Health Sciences, Kampala, Uganda; [6]Department of Community and Public Health, Faculty of Health Sciences, Busitema University, Mbale, Uganda; [7]Department of Medicine, School of Medicine, College of Health Sciences, Makerere University, Kampala, Uganda

Correspondence: Ronald Kasoma Mutebi, Department of Medicine, Mengo Hospital, PO BOX 7161, Kampala, Uganda, Email dr.rkmutebi@gmail.com

Introduction: Dolutegravir-based anti-retroviral therapy (ART) regimens were rolled out as first line HIV treatment in Uganda due to their tolerability, efficacy and high resistance barrier to human immunodeficiency virus (HIV). They have however been associated with weight gain, dyslipidemia and hyperglycemia which are cardiometabolic risk factors of hypertension. We assessed the prevalence and factors associated with hypertension among adults on dolutegravir regimens.

Methods: We conducted a cross-sectional study on 430 systematically sampled adults on dolutegravir-based ART for $\geq$ 6 months. Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg or history of use of antihypertensive agents.

Results: The prevalence of hypertension was 27.2% (117 of 430 participants) [95% CI: 23.2–31.6]. Majority were female (70.7%), the median age 42 [34, 50] years, with body mass index (BMI) $\geq$ 25 kg/m^3 (59.6%) and median duration on DTG-based regimens of 28 [15, 33] months. Being male [aPR: 1.496, 95% CI: 1.122–1.994, P = 0.006], age $\geq$ 45 years [aPR: 4.23, 95% CI: 2.206–8.108, P < 0.001] and 35–44 years [aPR: 2.455, 95% CI: 1.216–4.947, P < 0.012] as compared with age < 35 years, BMI $\geq$ 25 kg/m^3 [aPR: 1.489, 95% CI: 1.072–2.067, P = 0.017] as compared with BMI < 25 kg/m^3, duration on dolutegravir-based ART [aPR: 1.008, 95% CI: 1.001–1.015, P = 0.037], family history of hypertension [aPR: 1.457, 95% CI: 1.064–1.995, P = 0.019] and history of heart disease [aPR: 1.73, 95% CI: 1.205–2.484, P = 0.003] were associated with hypertension.

Conclusion: One in every four people with HIV (PWH) on dolutegravir-based ART has hypertension. We recommend the integration of hypertension management in the HIV treatment package and policies to improve existing supply chains for low cost and high-quality hypertension medications.

Keywords: hypertension, dolutegravir, HIV

Introduction

Globally, 36 million adults live with HIV (PWH). Sub-Saharan Africa (SSA) alone accounts for more than 60% of this global HIV burden. In 2020, there were an estimated 1.7 million new infections in SSA which accounted for almost 70% of the global total of new HIV infections. With the improved strategy against HIV such as the test and treat strategy, more

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than 90% of PWH in Uganda have access to ART.[1] As survival rates improve due to ART, long-term HIV treatment has been associated with emerging challenges such as cardiovascular diseases, majorly hypertension.[2]

Among PWH, the burden of hypertension varies in different regions of the world.[2–5] However, SSA carries the biggest part of this dual HIV–hypertension burden in addition to epidemic poverty.[5,6] Many risk factors such as older age, black ethnicity, male gender, modifiable factors such as obesity, smoking and alcohol use have been attributed to hypertension among PWH.[6] Other HIV-related factors such as some ART agents, longer effects of ART and duration of HIV infection have also been reported to be associated with hypertension.[7]

Despite its recommendation by the World Health Organization (WHO) for first-line ART regimens, dolutegravir, an integrase inhibitor, has been associated with serious adverse drug effects such as obesity and hyperglycemia.[8–13] These are cardiometabolic risk factors of hypertension hence posing an increased risk of hypertension among PWH on dolutegravir.

Dolutegravir-based regimens have widely been rolled out in various HIV clinics as a first-line treatment option for HIV since 2018 in Uganda and other countries in SSA.[14,15] This implies that the population of PWH on dolutegravir is large as many were switched from other regimens such as efavirenz-based regimens to dolutegravir. This was not only due to superiority, low potential for drug interaction and high genetic barrier resistance against HIV of dolutegravir regimens over other regimens such as efavirenz but also their tolerability in various communities.[15,16]

With paucity of data on the prevalence of hypertension among PWH on dolutegravir, our study aimed to determined prevalence of and factors associated with hypertension among adults on dolutegravir-based ART in Uganda.

Methods

Study Design and Setting

We conducted a cross-sectional hospital-based study between October and December 2021 among adults on dolutegravir-based ART at the counseling and home care department (CHCD) in Mengo Hospital. Mengo Hospital is a Kampala-based, private not for profit missionary hospital located in Rubaga division. CHCD is a specialized HIV outpatient clinic which offers free HIV/AIDS testing, treatment and monitoring, and with more than 7000 of 8800 PWH on dolutegravir-based ART. It consists of a team of various cadres among whom are clinicians, nurses and laboratory staff who have received training in HIV management and care. CHCD receives supplies and medicines from the government of Uganda like all other HIV clinics hence there is a steady supply. It mostly serves clients from Rubaga division and other surrounding villages.

Study Population

We included all adults (≥ 18 years) PWH on dolutegravir-based ART regimens who were receiving routine HIV care with no previous history of hypertension prior to start of a dolutegravir-based ART regimen and had provided a written informed consent. We excluded critically ill and pregnant mothers due to the hospital referral per protocol to specialized departments.

Using the Kish Leslie formula with a hypothesized prevalence of hypertension at 50% for maximum sample size calculation, level of significance at 5%, desired level of power at 80% and 10% non-response rate, a sample of 430 participants was obtained.[17] Every fourth patient in the register for the clinic day was enroled following systematic sampling.

Data Collection Procedure and Study Procedure

Trained research assistants administered the pretested questionnaires and performed the physical measurements. We used the questionnaire to collect data on sociodemographic, behavioral, and clinical characteristics. Sociodemographic and behavioral factors included age, sex, marital status, education status, employment status, history of smoking, alcohol use since start of dolutegravir-based ART and physical activity. Clinical factors included current WHO stage, self-report of family history of DM and history since dolutegravir start of diabetes mellitus (DM) or cardiovascular disease (CVD).

Using a data abstraction tool, we also collected data on recent viral load, duration on DTG and the current ART regimen from both the electronic database and also from the physical clients' files.

Blood pressure was measured using a validated electric powered automated blood pressure monitor (SECA blood pressure monitor) 10 minutes after rest while the patient was seated in a quiet office and 5 minutes between each measurement. The measurements were done on the right arm using an appropriate cuff size of an OMRON device. Height and weight were measured twice using SECA 769 digital column scale in meters and kilograms, respectively while patient was standing in an upright position without shoes, parallel to the digital column and perpendicular to the weight scale. We recorded an average of each two readings into the database for analysis. Participants on dolutegravir-based ART scheduled for a clinic visit day were requested to fast overnight until after having a blood sample taken by the health worker at the CHCD in order to measure their fasting blood sugar (FBS). The blood sample was collected from the non-dominant arm or on patient's preference. FBS and lipid profile tests were performed using EMATE glucometer (units: mmol/l) on site and COBAS e311 (units: mmol/l) in Mulago Hospital biochemistry laboratory, respectively.

Hypertension was defined based on the 2020 International Society of Hypertension Global Hypertension Practice Guidelines as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg and/or self-report of use of anti-hypertensive medication.[18]

Body mass index: Body mass index was calculated as division of the average weight in kilograms against the square of height in meters. BMI < 25 kg/m^3 and ≥ 25 kg/m^3 were classified as normal and overweight/obese, respectively.

Statistical Analysis

All filled data collection forms were checked for completion, double data entry using EpiData 3.0 and was cleaned in Excel. Analysis was done in STATA version 14.0. Continuous variables were summarized as medians (interquartile range) while categorical variables as proportions. The prevalence was calculated as the proportion of hypertension among participants. Data are presented in tables. At bivariable and multivariable analysis, a generalized linear model regression of the Poisson family with a log link (modified Poisson) using robust standard errors was performed since the prevalence of hypertension was more than 10%.[19] Variables with a P-value of ≤ 0.2 at bivariable analysis and those known in literature such as sex and body mass index were run in the multivariable regression to determine the association of various predictor variables with hypertension. Collinearity, interaction and confounding were assessed during the analysis.

Results

Description of the Participants

Of the 430 participants, the majority were female (n = 301, 70.7%), 41.1% were aged ≥ 45 years, 86 (20%) reported to have ever used alcohol, 8 (1.9%) reported to have used tobacco, 255 (59.6%) had a BMI ≥ 25 kg/m^3 while 103 (23.9%) and 158 (36.7%) had a family history of diabetes and hypertension, respectively. Nearly all the participants (423, 98.4%) have their HIV viral load suppressed, 416 (96.7%) on tenofovir/lamivudine/dolutegravir and 287 (67.4%) had been on dolutegravir-based ART regimen for more than 24 months with a median duration of 28 [15, 33] months (Table 1).

Prevalence of Hypertension

From the study, the prevalence of hypertension was 27.2% (117 of 430 participants) with a 95% confidence interval (CI) of 23.2–31.6% (Figure 1). Among the hypertensive participants, the median systolic and diastolic pressure readings were 142 [130, 152] mmHg and 90 [84, 97] mmHg, respectively whereas those among the normotensive participants were 115 [107, 122] mmHg and 71 [66, 79] mmHg, respectively. The prevalence was higher among males at 36.5% [95% CI: 28.5–45.4] as compared with females at 23.4% [95% CI: 18.9–28.5], those with body mass index ≥ 25 kg/m^3 at 31.4% [95% CI: 26.0–37.4] as compared with those with < 25 kg/m^3 at 21.4% [95% CI: 15.9–28.2] and those who had been on dolutegravir-based ART for ≥ 2 years at 33.1% [95% CI: 27.9–38.8] as compared with those < 2 years at 15% [95% CI: 9.9–22] (Table 1).

Table 1 Hypertension and Its Associated Factors Among the Study Participants

Variable	Total (%)	Hypertension n (%)		P value
		No	**Yes**	
	430	313 (72.8)	117 (27.2)	
Sex				
Female	304 (70.7)	233 (76.6)	71 (23.4)	
Male	126 (29.3)	80 (63.5)	46 (36.5)	0.005
Age				
< 35	112 (26.1)	103 (92.0)	9 (8.0)	
35–44	140 (32.5)	109 (77.9)	31 (22.1)	
≥ 45	178 (41.4)	101 (56.7)	77 (43.3)	< 0.001
Marital status				
Single	200 (46.5)	158 (79.0)	42 (21.0)	
Married	175 (40.7)	123 (70.3)	52 (29.7)	
Separated/divorced	34 (7.9)	19 (55.9)	8 (44.1)	
Widowed	21 (4.9)	13 (61.9)	8 (38.1)	0.014
Body Mass Index				
< 25	173 (40.4)	136 (78.6)	37 (21.4)	
≥ 25	255 (59.6)	175 (68.6)	80 (31.4)	0.023
History of alcohol use				
No	344 (80.0)	252 (73.3)	92 (26.7)	
Yes	86 (20.0)	61 (70.9)	25 (25.1)	0.665
History of smoking*				
No	422 (98.1)	309 (73.2)	113 (26.8)	
Yes	8 (1.9)	4 (50.0)	4 (50.0)	0.144
Family history of diabetes				
No	327 (76.1)	244 (74.6)	83 (25.4)	
Yes	103 (23.9)	69 (67.0)	34 (33.0)	0.129
Family history of hypertension				
No	272 (63.3)	215 (79.0)	57 (21.0)	
Yes	158 (36.7)	98 (62.0)	60 (34.0)	< 0.001
Low density lipoprotein				
< 2.56 mmol/l	249 (57.9)	188 (75.5)	61 (24.5)	
≥ 2.56 mmol/l	181 (42.1)	125 (69.1)	56 (30.9)	0.138
High density lipoprotein				
≥ 1.3 mmol/l	104 (24.2)	76 (73.1)	28 (26.9)	
<1.3 mmol/l	326 (75.8)	237 (72.7)	89 (27.3)	0.94
Triglycerides				
< 1.685 mmol/l	343 (79.8)	263 (76.7)	80 (23.3)	
≥ 1.685 mmol/l	87 (20.2)	50 (57.5)	37 (42.5)	< 0.001
Total cholesterol				
< 5.13 mmol/l	347 (80.7)	258 (74.4)	89 (25.6)	
≥ 5.13 mmol/l	83 (19.3)	55 (66.3)	28 (33.7)	0.137
Fasting blood glucose				
< 7 mmol/l	393 (92.3)	288 (73.3)	105 (26.7)	
≥ 7 mmol/l	33 (7.7)	22 (66.7)	11 (33.3)	0.412
Viral load*				
Suppressed	422 (98.1)	308 (73.0)	114 (27.0)	
Non suppressed	8 (1.9)	5 (62.5)	3 (37.5)	0.509
Duration on dolutegravir (years)				
< 2	140 (32.6)	119 (85.0)	21 (15.0)	
≥ 2	290 (67.4)	194 (66.9)	96 (33.1)	< 0.001

(*Continued*)

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Table I (Continued).

| Variable	Total (%)	Hypertension n (%)		P value
		No	**Yes**	
History of cardiac disease				
No	409 (95.1)	308 (75.3)	101 (24.7)	
Yes	21 (4.9)	5 (23.8)	16 (76.2)	< 0.001

Note: *Fisher's exact value.
Abbreviations: n, number of participants; CI, confidence intervals; P value, Pearson's chi square value.

The majority of the participants with hypertension were aged ≥ 45 years, had elevated low- and high-density lipoproteins, elevated triglycerides and fasting blood glucose. From the sub-group analysis, 100 (23.3%) and 96 (22.3%) had stage 1 and 2 hypertension, respectively, based on the American Heart Association Guidelines 2020 (Table 2).

Factors Associated with Hypertension

At multivariate analysis, the final model only included factors that were significant ($P < 0.05$). At multivariate analysis, being male [aPR: 1.496, 95% CI: 1.122–1.994, P = 0.006], age of 35–44 years [aPR: 2.455, 95% CI: 1.219–4.947, P = 0.012], age ≥ 45 years [aPR: 4.23, 95% CI: 2.206–8.108, P < 0.001], body mass index ≥ 25 kg/m^3 [aPR: 1.489, 95% CI: 1.072–2.068, P = 0.017], duration on dolutegravir-based ART [aPR: 1.008, 95% CI: 1.001–1.0152, P = 0.037], family history of hypertension [aPR: 1.457, 95% CI: 1.065–1.995, P = 0.019] and history of heart disease [aPR: 1.73, 95% CI: 1.205–2.484, P = 0.003] were significantly associated with hypertension (Table 3).
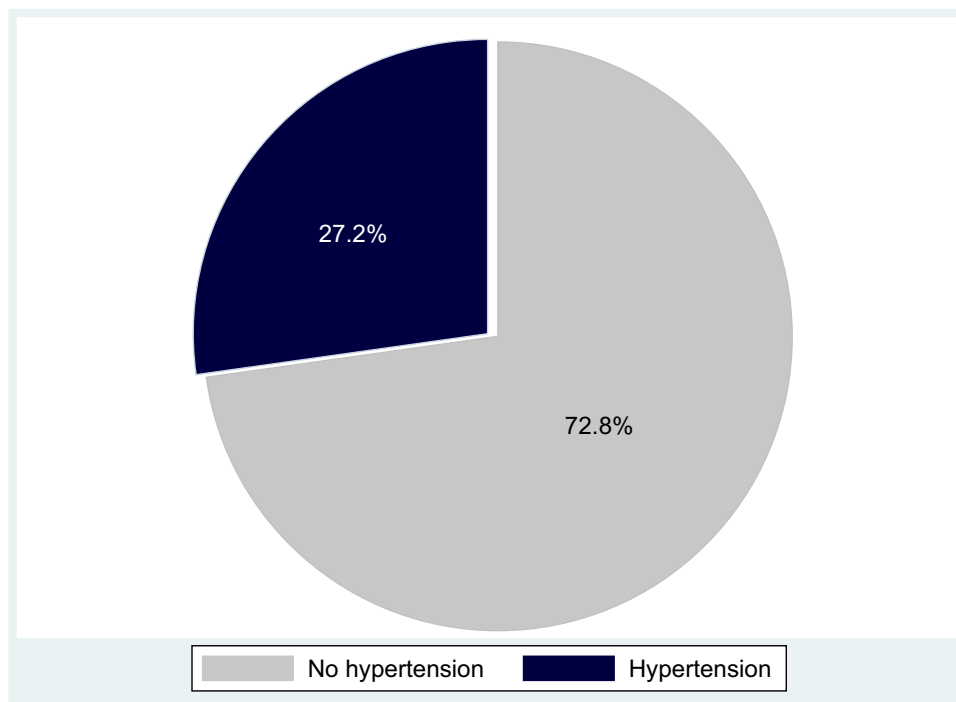
Figure I Prevalence of hypertension among the study participants.

Table 2 Hypertension Based on AHS Guidelines 2020 (Sub-Analysis)

Variable	n	%
Blood pressure		
Normal BP	168	39.1
Elevated BP	66	15.3
Stage 1 hypertension	100	23.3
Stage 2 hypertension	96	22.3

Note: n - frequency, % proportion in percentage.
Abbreviation: BP, blood pressure.

Table 3 Bivariate and Multivariate Analyses of the Factors Associated with Hypertension Among the Study Participants

Variable	cPR (95% CI)	P value	aPR (95% CI)	P value
Sex*				
Female	1		1	
Male	1.563 (1.149–2.126)	0.004	1.496 (1.122–1.994)	0.006
Age (years)*				
< 35			1	
35–44	2.756 (1.368–5.55)	0.005	2.455 (1.216–4.947)	0.012
≥ 45	5.383 (2.812–10.307)	< 0.001	4.230 (2.206–8.108)	<0.001
Body mass index (kg/m^3)*				
< 25	1		1	
≥ 25	1.467 (1.045–2.059)	0.027	1.489 (1.072–2.067)	0.017
Duration on dolutegravir (months)*				
	1.011 (1.005–1.0182)	< 0.001	1.008 (1.001–1.015)	0.037
Family history of hypertension*				
No	1		1	
Yes	1.812 (1.335–2.459)	<0.001	1.457 (1.064–1.995)	0.019
History of heart disease*				
No	1		1	
Yes	3.085 (2.301–4.137)	< 0.001	1.730 (1.205–2.484)	0.003
High density lipoproteins				
< 1.3 mmol/l	1			
≥ 1.3 mmol/l	0.986 (0.686–1.418)	0.94		
Low density lipoproteins*				
< 2.56 mmol/l	1			
≥ 2.56 mmol/l	1.263 (0.929–1.719)	0.138		
Triglycerides*				
< 1.685 mmol/l	1			
≥ 1.685 mmol/l	1.823 (1.336–2.489)	<0.001		
Total cholesterol*				
< 5.13 mmol/l	1			
≥ 5.13 mmol/l	1.315 (0.926–1.869)	0.126		
Fasting blood glucose				
< 7 mmol/l	1			
≥ 7 mmol/l	1.248 (0.749–2.078)	0.395		
History of diabetes				
No	1			
Yes	0.733 (0.126–4.267)	0.729		

(*Continued*)

Table 3 (Continued).

Variable	cPR (95% CI)	P value	aPR (95% CI)	P value
Family history of diabetes*				
No	I			
Yes	1.301 (0.933–1.813)	0.121		
Marital status*				
Single	I			
Married	1.415 (0.994–2.014)	0.054		
Separated/divorced	2.101 (1.32–3.342)	0.002		
Widowed	1.814 (0.987–3.334)	0.055		
Smoking*				
No	I			
Yes	1.867 (0.917–3.804)	0.085		
Alcohol use				
No	I			
Yes	1.087 (0.748–1.58)	0.662		
Viral load				
Non suppressed	I			
Suppressed	1.388 (0.559–3.446)	0.71		

Note: *Considered for multivariate analysis.
Abbreviations: cRP, crude prevalence ratio; aPR, adjusted prevalence ratio.

Discussion

In this cross-sectional study, the majority of the study participants had their HIV under control as evidenced by the magnitude of those with a suppressed viral load at 98.4%. The prevalence of hypertension among study participants on dolutegravir-based ART was 27.2% (95% CI: 23.2–31.6). It is fairly similar to that of Uganda's nationwide NCD risk factor survey data conducted in 2014.[20] The prevalence in the study was different from the sub-analysis prevalence of stage 2 hypertension (Table 2) because participants who had a normal blood pressure though on antihypertensive agents were included, hence a higher study prevalence.

Despite the fact that females dominated the study, the prevalence was higher among males. It was also higher in those with a family history of hypertension and those with a BMI of 25 kg/m^3 and above.

Being male was associated with hypertension among the study participants. This finding is similar to what was found in other studies among PWH.[21,22] This is not surprising as estrogen is believed to have a positive impact on the vasodilation of the vessels hence subsequent control of hypertension.[23] This implies that menopause is a major blow in every aging woman's life since estrogen lowers.[23]

Body mass index $\geq$ 25 kg/m^3 was significantly associated with hypertension. These findings are similar to other studies conducted in various countries such as Kenya, Tanzania, South Africa, Tunisia and China.[24–27] This is not surprising as nearly 60% of the participants had a body mass index $\geq$ 25 kg/m^3. Overweight and obesity are traditionally defined by accumulation of body fat above 20% expressed by a BMI between 25–29.9 kg/m^3 and $\geq$ 30 kg/m^3, respectively.[28] Obesity has been listed among a sole risk factor of hypertension and other illnesses such as diabetes mellitus.[28,29] Despite the unclear dolutegravir–obesity mechanism, various studies have reported association of over-weight, obesity and dolutegravir.[12,30] This implies that prevention programs focusing on weight reduction and healthy diet are key in reducing overweight and obesity among PWH on dolutegravir.

Duration on dolutegravir-based ART was significantly associated with hypertension among the study participants. Others studies have reported an association of a longer duration ART with hypertension.[4,5] In another meta-analysis of HIV patients, it was revealed that longer duration of ART exposure was associated with an increased risk of hypertension.[31] The mechanism of how a longer duration on ART leads to hypertension is unclear. However, various hypotheses have been attributed to weight gain that could result from the specific regimens such as those with dolutegravir coupled with unhealthy

lifestyle habits such as physical inactivity and unchecked diet (excess carbohydrates).[32] Another hypothesis considers how the long-term exposure to ART leads to persistent activation of the immune system. Within the vascular system, high levels of elevated biomarkers such as interleukin 6 (IL-6) lead to vascular changes hence loss of elasticity that is key in vasodilation to maintain the vascular blood pressure.[33] It is not surprising that even from the sub-analysis, duration on dolutegravir above 24 months were associated with hypertension (Figure 2).

We also found that hypertension was associated with increasing age. Various changes occur with increasing age. They include loss of elastin, collagen deposition and protein glycation in the vessel walls. These lead to thickening and stiffening of the vessels hence diastolic and systolic hypertension.[34–36] With the improved survivorship due to ART, a bigger population of PWH are aging which makes them candidates for hypertension. Various studies have shown how increasing age is associated with hypertension.[21,24,27,37,38]

History of cardiac disease was also significantly associated with hypertension. Similar studies of patients on other ART regimens have too been reported to be associated with hypertension.[39]

There was no significant association between hypertension and triglycerides, low density lipoproteins, high density lipoproteins, total cholesterol, history of smoking, alcohol use, ART regimen, marital status, education status, employment status and baseline CD4. This could be explained by the study design being cross sectional and the presence of selection bias as we only selected those on dolutegravir.

In a sub-analysis done with hypertension based on the American Heart Association definition, 196 (45.6%) participants were classified to have stage 1 or stage 2 hypertension. It also reveals that 66 (15.4%) had elevated blood pressure (systolic blood pressure 120–129 mmHg and diastolic blood pressure < 80 mmHg).[40] The above prevalence is
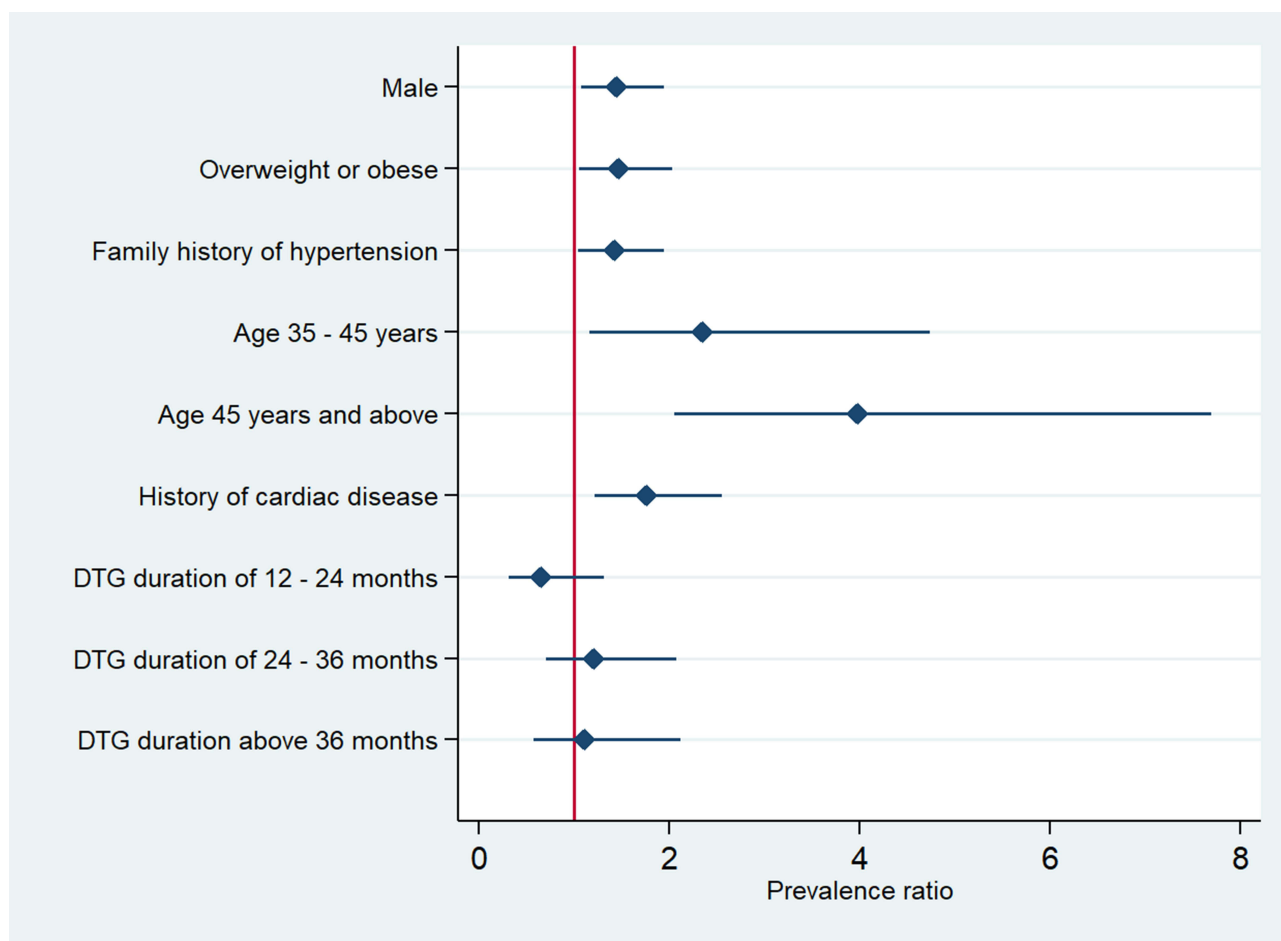

Figure 2 A graph of the multivariable analysis, DTG, dolutegravir.

different from the 27.2% obtained in the study. This is because patients on antihypertensives are not classified as hypertensive as per the study's definition.

Our study had some strengths. It was conducted in a large HIV treatment center from one region. The majority of the participants were stable on ART as evidenced by the suppressed viral load. This implies that it likely represents the general population on ART due to a nationwide scale up of the PWH on dolutegravir in Mengo Hospital. There were potential limitations in our study. Being a cross-sectional study, our study was limited by the inability to assess the temporal relationships. Other limitations include: missing data during abstraction, a possibility of recall bias during interviews, lack of control group hence compromised internal validity, selection bias as all participants were recruited from hospital and also some patients not reporting their true fasting status. Measurements of hypertension 10 minutes apart contrary to the conventional 6 hours apart may give misleading results and hence overestimate or underestimate the true prevalence.

Conclusions

In summary, our study findings reveal that one in every four adults on dolutegravir-based ART is hypertensive. This similar to Uganda's general population hypertension prevalence. We recommend integration and strengthening of screening and management of hypertension among PWH on ART. Future research for cost-effective interventions such as routine screening on every visit in order to reduce the burden of hypertension among PWH is needed.

Patient and Public Involvement

Patients did not participate in any aspect of the research study such as design, methods, interpretation of findings or contribute to the writing of this paper.

Data Sharing Statement

The data from this study will be available on request to the corresponding author.

Ethics

The study was approved by Makerere University School of Medicine Research Ethics Committee (SOMREC) with approval number: MAK-SOMREC-2021-178. Mengo Hospital provided the administrative authorization. Informed consent was obtained from all eligible participants using an informed consent form by their signature or thumb–print while others were signed by a witness for those who could not read and write. This study complies with the Declaration of Helsinki.

Consent for Publication

All authors consented to have the manuscript with the attached documents published.

Disclosure

There was no conflict of interest as declared by the authors.

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