The Prevalence of Hypertension and its association with HIV related factors in HIV patients on ART, Bagamoyo District, Eastern Tanzania

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Abstract

Effective use of antiretroviral therapy (ART), has greatly upgraded the quality of life and survival of individuals suffering from HIV/AIDS. However, the incidence rate of hypertension is reported growing up. The overall aim was to find out the prevalence of hypertension and its association with HIV related factors in HIV patients on ART, in Bagamoyo district Tanzania. This was a cross-sectional study of HIV patients on ART visiting care and treatment clinics. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg or being on medications for hypertension. Logistic regression was applied during the analysis. The study investigated 328 HIV patients on ART, 64.6% were female, and 92.68% on non-protease inhibitors medication and 14% had a prior history of TB in the past 5 years. The overall prevalence of hypertension was 29.3% and was significantly and positively associated with increasing age (years): 40-59, 3.40 (1.80-6.41) 0.001, ≥ 60, 9.25 (3.96-21.60) 0.001, obesity 3.63 (1.60-8.26) 0.002, non-protease inhibitors 4.31 (1.16-16.03) 0.029 and tenofovir 4.27 (1.15-15.96) 0.031. However, duration since HIV diagnosed of 5-9 years, 0.82 (0.44-1.51) 0.521, ≥ 10 years, 0.61 (0.27-1.35) 0.222 and recent CD4+cell count of 100-349 0.90(0.30-2.70) 0.845, 350-499, 1.04(0.34-3.16) 0.940 were found not associated with increased odds of having hypertension. In conclusion, the prevalence of hypertension in HIV patients on ART was 29.3% and it was significantly and positively associated with increasing age, obesity, and non-protease inhibitors. Regular monitoring of blood pressure is crucial among HIV/AIDs patients.

Introduction

Effective use of antiretroviral therapy (ART), has greatly upgraded the quality of life and survival of individuals suffering from HIV/AIDS (Chastain, Henderson & Stover, 2015). However, the incidence rate and mortality from cardiovascular risk factors including hypertension are reported to growing up (Xu, Chen & Wang, 2017). For example, in a recent meta-analysis study prevalence of hypertension was 34.7% among HIV patients on ART compared to 12.7% in ART naïve individuals (Xu *et al.*, 2017). In Tanzania, the prevalence of hypertension among HIV patients on antiretroviral therapy has been reported to be 28.3% (Peck *et al.*, 2014). The risks of hypertension in HIV patients can be either traditional (established risks) or non-traditional. Non-traditional risks constitute HIV related factors such as inflammations, ART toxicity, and immune response (Madhur *et al.*, 2016). For instance, tenofovir an ART belongs to non-protease inhibitors class has been reported to contribute to hypertension due to its ability to cause renal failure and therefore secondary hypertension (Ojeh *et al.*, 2018). Also, higher CD+ cell count (following immune reconstitution after initiation of ART) has been reported to associate with hypertension in

adults HIV infected individuals (Peck *et al.*, 2014). Despite that, the contributions of HIV related factors to hypertension have not been extensively investigated in Tanzania.

Therefore, we conducted a cross-sectional to explore the prevalence of hypertension and its association with HIV related factors in HIV patients on ART while adjusting for other covariates in Bagamoyo district, eastern Tanzania. We aim to contribute to the body of knowledge regarding hypertension among HIV patients in Tanzania.

Materials and methods

Study design and location
This was cross-sectional involving HIV patients who were on ART conducted between March and May 2019, in Bagamoyo district, eastern Tanzania. The district is located in the coastal region which has an HIV prevalence rate of 6.4% (Ministry of Health, 2016). Data were collected from 2 public clinics (Bagamoyo district hospital and Kerege health center) which were purposively selected based on their relatively large size and presence of established patient's record database (computer-based record system). The two clinics provide care and treatments based on the national HIV/AIDS guidelines of Tanzania (Ministry of Health, 2017).

Inclusion and exclusion criteria
The inclusion criteria were being HIV positive, aged above 18, on ART, who gave consent for participation. Women who reported to be pregnant and those on contraceptive pills were excluded.

Sample Size estimates
To calculate the sample size the formula below was used:

$$N=P(1-P)(Z/E)$$

Whereby margin of error (E) = 5%, P=Prevalence

N=estimated required sample size, Z= 95% confidence interval = 1.96, attrition of 10% for missing data. Prevalence (P) 26.2% from a closely related study by Kagaruki *et al*. 2014

$0.262(1-0.262)(1.96/0.05)2$, margin of error (E) = 5%, P=Prevalence

Sample size = 328

Blood pressure measurement and definition
Blood pressure was measured by trained health care workers as per required standards in the right arm, utilizing a mercury sphygmomanometer of appropriate size, with individual participants in sitting in a relaxed position and upright position (Joint National Committee, 2004). Two readings were taken 10 minutes apart and an average of two results was turned to account in the final analysis. Hypertension was defined as systolic blood pressure (SBP) of ≥ 140 mmHg, diastolic blood pressure (DBP) of ≥ 90 mmHg (Joint National Committee, 2004) or taking ant-hypertensive medications regardless of the blood pressure value measured on the day of data collection.

Anthropometric measurement
Bodyweight (precision of 0.1 kg) was weighed using the patients weighing machine (seca scale) by trained health care workers, with individual participants at minimal clothes and wearing no shoes. Body height was assessed using a stadiometer (precision of 0.1 cm) participant wearing no shoes. Body mass index (BMI) was computed utilizing the formula: weight in kilogram (kg) divided by the square of height in meters (Kg/m^2). BMI was classified and defined using the WHO protocol as follows; underweight $< 18.5\,kg/m^2$, normal body weight $18.5-24.9\,kg/m^2$, overweight $25-29.9\,kg/m^2$, and obese $\geq 30\,kg/m^2$ (World Health Organization, 2004).

Sociodemographic, HIV related factors collection and definition
The structured questionnaire administered by trained health care workers was used to collect the sociodemographic, family history of hypertension, current history of TB and history of TB in the past 5 years.

In addition to the individual interview, the following information was extracted directly from patient record card or computerized patients' database system: duration since HIV diagnosed, recent CD4+cell count, the current class of ART, and individual cART.

Duration since HIV diagnosis was defined as the time in years at which HIV diagnosis was confirmed as it was documented in patient record cards. Recent CD4+cell count was

defined as the CD4+T cell count measured in the past 6 months.
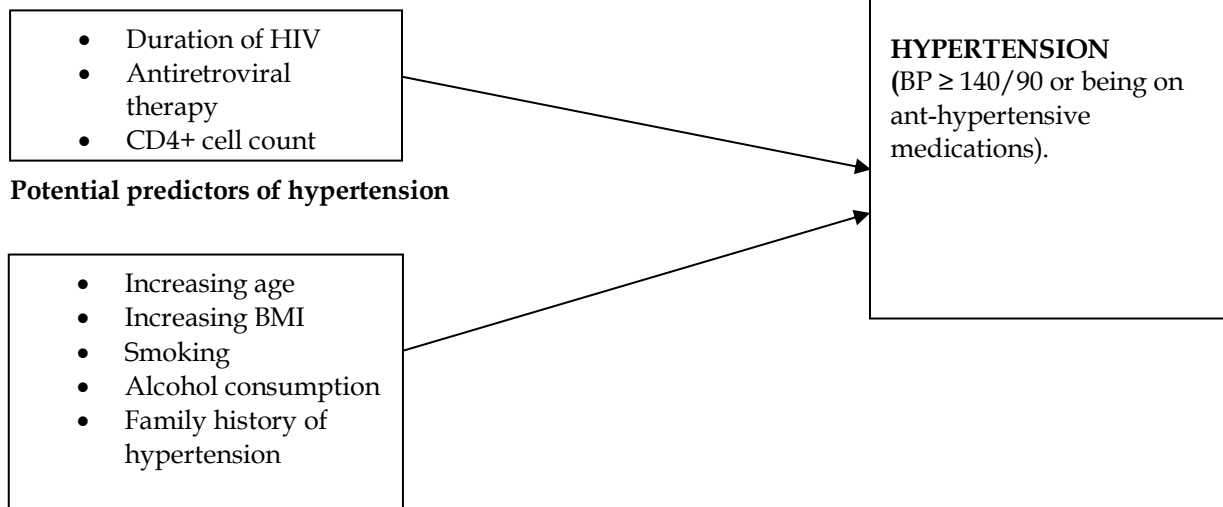
Exposure, outcome and confounding Variables
The primary outcome variable of interest was hypertension defined as blood pressure ≥ 140/90 mmHg, or being on medications for hypertension. Individuals with blood pressure ≥ 140/90 mmHg and those who self-reported the use of ant-hypertensive medication were all added to form a primary outcome of interest (hypertension).

Exposure variables of interest in the current analysis were: duration since HIV diagnosis, recent CD4+cell count, the current class of ART and individual cART. The potential confounders included during the analysis were: age, sex, obesity, and family history of hypertension.

Exposure variable of interest
Outcome variable

- Duration of HIV
- Antiretroviral therapy
- CD4+ cell count

Potential predictors of hypertension

- Increasing age
- Increasing BMI
- Smoking
- Alcohol consumption
- Family history of hypertension

HYPERTENSION
(BP ≥ 140/90 or being on ant-hypertensive medications).

Data management and analysis
Data was gathered by a means of a structured questionnaire and then entered into an Excel sheet. Before data was entered in the Excel sheet, a completed questionnaire was reviewed for completeness and clarity. Before data analysis, another review was done for errors, missing data, and inconsistencies. The analysis was done using STATA version 13. We included 328 participants in the final analysis and 33 participants had missing data regarding the recent CD4+cell count. A descriptive analysis (percentage for categorical variables) was used to summarize the data.
Logistic regression was executed to check for an association between HIV related factors and hypertension. Variables found to have a p-value less than 0.05 in univariate analysis were examined in a multivariate model of logistic regression. Models were adjusted for potential confounders with p-value < 0.05 (age, BMI and family history of hypertension) and ART as a class because of a possible biological plausibility. Sex was included in multivariate analysis as a forced variable, because sex is a basic demographic, therefore it's very important to control in the final model. In multivariate analysis, variables were added by a forward selection technique with the variables of greater theoretical significance entered first. For logistic regression, models we assumes linearity of exposure variables and log odds and variables to be independent of each other.

Ethical approval; The protocol of the study was reviewed and certified by the research ethics committee of the Ifakara Health Institute, Bagamoyo district executive director office as well as the authority of the respective health facility. Written informed consent was attained from each of the participants ahead of data gathering.

Results

Sociodemographic factors and clinical profile of the participants
A total of 328 study participants were included in the analysis. Out of 328 participants, 212 (64.6%) were females and 116 (35.4%) male (Table 1). In the descriptive analysis of the age in years, 132 (40.24%), 151 (46.06%) and 45

(13.72%) were individuals aged 18-39 years, 40-59 years, and ≥ 60 years, respectively (Fig. 2). Out of 328 participants, 213 (64.9%) were peasants and 115 (35.06%) non-peasants (Table 1).

In further analysis out of 328 participants, 89 (25%) were either obese or overweight, and 161 (49%) of the participants diagnosed with HIV within the last 5 years (Table 1). Current alcohol drinkers and cigarette smokers were observed in 42 (12.8%) and 17 (5.18%) respectively (Table 1).

The HIV related factors characteristics of the participants were as follows; Out of 328 participants, 161 (49.09%), 110 (33.54%) and 57

(17.38%) had duration since HIV diagnosis of < 5 years, 5-9 years and ≥ 10 years respectively (Table 1). There were 304 (92.68%) patients on non-protease inhibitors and 24 (7.32%) on protease inhibitors as the class of ART (Table 2). The majority of patients 285 (86.89%) were on tenofovir based cART and the rest had been either on zidovudine or atazanavir (Table 1).

Data on the recently CD4+ cell was available in 25 (8.47%), 75 (25.42%), 75 (25.42%) and 120 (40.68%) of the patients with CD4+ cell count of < 100, 100-349, 350-499 and ≥ 500 respectively (Table 1). However, there were missed data for CD4+cell count in 33 participants, which is equivalent to 10 percent of all the participants (Table 1).

Table 1: *Socio demographic and clinical profile of the participants*

Factors of interest	n (%)
Age (Years)	
18-39	132 (40.24)
40-59	151 (46.06)
≥ 60	45 (13.72)
Sex	
Female	212 (64.63)
Male	116 (35.37)
Occupation	
Peasants	213 (64.94)
Others	115 (35.06)
Alcohol drinker	42 (12.80)
Current cigarette smokers	17 (5.18)
BMI (kg/m²)	
Underweight (<18.5)	46 (14.02)
Normal weight (18.5−24.9)	193 (58.84)
Overweight (25−29.9)	51 (15.55)
Obese (≥ 30)	38 (11.59)
Duration since HIV diagnosed (years)	
< 5	161 (49.09)
5−9	110 (33.54)
≥ 10	57 (17.38)
Recently CD4 +cell count(cell/μl)	
<100	25 (8.47)
100- 349	75 (25.42)
350−449	75 (25.42)
≥ 500	120 (40.68)

Current class of ART	
Protease inhibitors	24 (7.32)
Non-protease inhibitors	304 (92.68)
Individual cART	
Zidovudine	19 (5.79)
Tenofovir	285 (86.89)
Atazanavir	24 (7.32)
Overall	**328**

The prevalence of hypertension

In the current study, the overall prevalence of hypertension in HIV patients on ART was 29.3 % (Table 2). According to gender, the prevalence was 33 (28.5%) in males and 63 (29.7%) in females (Table 2). The prevalence of hypertension was higher in the individuals aged ≥ 60 years 24 (53.3%), compared to 50 (33.1%) in the individuals aged 40-59 years, and 22 (16.7%) in the individuals aged 18-39 years (Table 2). Regarding the BMI, the prevalence of hypertension was 55.3%, 39.2%, 27.5% and 4.4% in obese, overweight, normal weight and underweight respectively (Table 2).

Furthermore, during the descriptive analysis of HIV related factors, the prevalence of hypertension was 28%, 30.7%, 29.3% and 30.0% in the participants with the CD4+ cell counts of < 100, 100-349, 350-499 and ≥ 500 respectively (Table 2). Also, the prevalence of hypertension was 12.5% and 30.6% in the participants who were on protease inhibitors and non-protease inhibitors respectively (Table 2).

Table 2: *Sociodemographic and HIV related factors associated with hypertension*

Factors of interest	Hypertensive n (%)	Non hypertensive n (%)	TOTAL
Age (Years)			
18-39	22 (16.7)	111 (83.3)	132
40-59	50 (33.1)	101 (66.9)	151
≥ 60	24(53.3)	21 (46.7)	45
Sex			
Female	63 (29.7)	149 (70.3)	212
Male	33(28.5)	83 (71.5)	116
Occupation			
Peasants	63 (29.6)	150 (70.4)	213
Others	33 (28.7)	82 (71.3)	115
Alcohol drinker	13 (30.9)	29 (69.1)	42
Smoking cigarette	7 (41.2)	10 (58.8)	17
BMI (kg/m²)			
Underweight (<18.5)	2 (4.4)	44 (95.6)	46
Normal weight (18.5—24.9)	53 (27.5)	140 (72.5)	193
Overweight (25—29.9)	20 (39.2)	31 (61.8)	51
Duration since HIV diagnosed (years)			
< 5	48 (29.8)	113 (70.2)	161
5—9	33 (30.0)	77 (70.0)	110
≥ 10	15 (26.3)	42 (73.7)	57

Recent CD4 +cell count(cell/µl)

<100	7 (28)	18 (72)	25
100- 349	23 (30.7)	52 (69.3)	75
350−449	22 (29.3)	53 (70.7)	75
≥ 500	36 (30.0)	84 (70.0)	120

Current class of ART

Protease inhibitors	3 (12.5)	21 (87.5)	24
Non- protease inhibitors	93 (30.6)	211 (69.4)	304

Individual cART

Zivodune	8 (42.1)	11 (57.9)	19
Tenofovir	85 (29.4)	204 (70.6)	289
Atazanavir	3 (12.5)	21 (87.50)	24
Overall	**96 (29.3)**	**232(70.7)**	**328**

BMI = body mass index, cART = combination antiretroviral therapy, CD4 = cluster of differentiation 4, HIV = human immunodeficiency virus.

Univariate analysis

During the univariate analysis, we used p-value < 0.05 to indicate a statistical significance (statistical threshold). In the univariate logistic regression analysis, the sociodemographic factors that significantly associated with increased odds of having hypertension were: increasing age, higher BMI, and family history of (Table 3). However, sex, occupation, current alcohol drinker and current cigarette smokers were not significantly associated with hypertension (Table 3).

About HIV related factors, univariate analysis revealed that the only factor significantly associated with increased odds of hypertension was zidovudine (Table 3). Duration since HIV diagnosis, CD4+cell count and tenofovir were not associated with increased odds of having hypertension and their association was statistically insignificant (Table 3).

Table 3: *Univariate logistic regression analysis of factors associated with hypertension.*

Factor of interest	n	Odds ratios (95% CI)	P value
Age (years)			
18-39	132	Reference	
40-59	151	2.48 (1.40-4.37)	0.002
≥ 60	45	5.71 (2.72-12.01)	0.001
Sex			
Male	116	Reference	
Female	212	1.06 (0.65-1.78)	0.809
Occupation status			
Peasant	213		
Non peasant	115	0.96 (0.58-1.58)	0.867
Alcohol drinker			
No	286	Reference	
Yes	42	1.10 (0.54-2.21)	0.797
Smoking cigarette			

	n	Odds ratios (95% CI)	P value
No	311	Reference	
Yes	17	1.75 (0.64-4.73	0.273
BMI (kg/m$^{2)}$)			
Normal weight (18.5—24.9)	193	Reference	
Underweight (<18.5)	46	0.12 (0.28-0.51)	0.004
Overweight (25—29.9)	51	1.70 (0.89-3.25)	0.105
Obese (≥ 30)	38	3.3 (1.6-6.66)	0.001
Family history of hypertension			
No	287	Reference	
Yes	41	2.64 (1.36-5.15)	0.004
Duration since HIV diagnosed (years)			
< 5	161	Reference	
5—9	110	1.01 (0.59-1.71)	0.974
≥ 10	57	0.84 (0.42-1.66)	0.617
Recent CD4 + cell count(cell/µl)			
<100	25	Reference	
100-349	75	1.13 (0.42-3.09)	0.801
350—499	75	1.07 (0.39-2.91)	0.899
≥ 500	120	1.10 (0.42-2.87)	0.842
Current class of ART			
Protease inhibitors	24	Reference	
Non-protease inhibitors	304	3.09 (0.89-10.6)	0.074
Individual cART			
Zidovudine	19	5.09 (1.12-23.14)	0.493
Tenofovir	289	2.98 (0.86-10.24)	0.001
Atazanavir	20	Omitted	

BMI = body mass index, cART = combination antiretroviral therapy, CD4 = cluster of differentiation 4, HIV= human immunodeficiency virus.

Multivariate analysis
In multivariate analysis, the sociodemographic characteristics associated with increased odds of hypertension and statistically significant were increasing age current smokers, and obesity (Table 4). Having a family history of hypertension was associated with increased odds of hypertension though the association was statistically insignificant (Table 4).

In further multivariate analysis, HIV related factors that were independently associated with increased odds of hypertension were non-protease inhibitors, and tenofovir (Table 4). On the other side, duration since HIV diagnosis, recent CD4+count and zidovudine, were not found to be associated with increased odds of hypertension and their association was statistically insignificant (Table 4).

Table 4: *Multivariate logistic regression analysis of factors associated with hypertension.*

Factor of interest	n	Odds ratios (95% CI)	P value
Age (years)			
18-39	132	Reference	
40-59	151	3.40 (1.80-6.41)	0.000
≥ 60	45	9.25 (3.96-21.60)	0.000
Sex			
Male	116	Reference	
Female	212	0.78 (0.43-1.40)	0.402

Occupation status			
Peasant	213	Reference	
Non-peasant	115	1.24 (0.69-2.24)	0.472
Current social behaviour			
Alcohol drinker			
No	286	Reference	
Yes	42	1.09 (0.54-2.21	0.797
Smoking cigarette			
No	311	Reference	
Yes	17	1.29 (0.57-2.92)	0.214
BMI (kg/m^2)			
Normal weight (18.5—24.9)	193	Reference	
Underweight (<18.5)	46	0.70 (0.02-0.32)	0.001
Obese (≥ 30)	38	3.63 (1.60-8.26)	0.002
Family history of hypertension			
No	287	Reference	
Yes	41	2.73 (1.27-5.84)	0.009
Duration since HIV diagnosed (years)			
< 5	161	Reference	
5—9	110	0.82 (0.44-1.51)	0.521
≥ 10	57	0.61 (0.27-1.35)	0.222
Recent CD4 + cell count(cell/μl) [c]			
<100	25	Reference	
100-349	75	0.90 (0.30-2.70)	0.845
350—499	75	1.04 (0.34-3.16)	0.940
≥ 500	120	1.25 (0.43-3.60)	0.677
Current class of ART			
Protease inhibitors	24	Reference	
Non -protease inhibitors	304	4.31 (1.16-16.03)	0.029
Individual cART			
Zidovudine	19	4.66 (0.91-23.99)	0.065
Tenofovir	285	4.27 (1.15-15.96)	0.031
Atazanavir	24	Omitted	

cART= combination antiretroviral therapy, CD4= cluster of differentiation 4, HIV= human immunodeficiency virus.

Discussion

In the current cross-sectional study, we found that the prevalence of hypertension among HIV patients on ART to be 29.3%% and it was similar among males and females. The high prevalence (29.3%) in the current study, is similar to the observed prevalence in previous studies in HIV patients on ART (Xu et al., 2017; Peck et al., 2014). The result together with those from previous studies strengthens the evidence that the prevalence of hypertension is greater among individuals living with HIV/AIDS on ART.

About HIV related factors, we found that duration since HIV diagnosis was not associated with increased odds of having hypertension, similar to what has been reported in a previous prospective observation cohort (Peck et al., 2014 ; Krauskopf et al., 2013). However, the result differs from what was reported by Medina-Torne et al. (2012). According to the analysed data by Medina-Torne et al. (2012), there was a positive and significant association between the duration of HIV infection and hypertension (Medina-torne et al., 2012). The difference might be explained by the way the duration of HIV was defined in the two settings. In the study by Medina-Torne et al. (2012), the duration of HIV was defined as the mid-point between the first HIV positive test and the last negative test to the time of data collection (Medina-torne et al., 2012). While the definition used in the current study was the time difference from the first seropositive and the time of study initiation.

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We also investigated whether there is an association between ART and hypertension. We found that non-protease inhibitors as the class of ART were significant and positively associated with hypertension, similar to what has been communicated in an observational study conducted in Uganda (Munderi, 2017). In further analysis of the individual ART combination therapy, we noted that tenofovir was significantly and positively associated with increased odds of having hypertension, similar to what has been reported in a previous study (Villa *et al.*, 2018). Tenofovir has been implicated to cause hypertension due to its kidney toxicity (Ru *et al.*, 2018). However, in the current study, we didn't measure the serum level of tenofovir to check for the tenofovir toxicity as well as renal function test, therefore we cannot conclude whether observed hypertension was directly linked to tenofovir toxicity.

Furthermore, we observed that zidovudine based combination therapy was associated with increased odds of having hypertension in the multivariate analysis though the association was not statistically significant, contrary to the findings in research conducted in North America which indicated a lack of significant association (Medina-Torne *et al.*, 2012). The contrasting results possibly are due to the dissimilarity in ethnicity, socio-demographic profiles and study design between two studies. The exact mechanism by which zidovudine may cause hypertension remains unclear. However, we have hypothesized that immune reconstitution syndrome following zidovudine-based combination may contribute to hypertension. On the other hand, the results of atazanavir were omitted from STATA output during univariate and multivariate logistic regression analysis possibly due to dependency of atazanavir as a variable with other antiretroviral medications variable (interdependency of variables). Therefore, we will not discuss atazanavir in this current study.

We also investigated the influences of the immune response on hypertension in HIV patients who were on ART. We found no significant association between recent CD4+cell count and hypertension, similar to what has been reported by previous studies (Furrer *et al.*, 2017; Dimala*et al.*, 2016; Medina-

torne *et al.*, 2012). However, our results differ from what has been reported in a previous study in north-western Tanzania which reported a positive association between hypertension and a high CD4+cellcount (Peck *et al.*, 2014). The difference might be explained by the inclusion criteria and definition for CD4+cell count used in the two studies. According to Peck *et al.* (2014), the inclusion criteria were being an HIV patient on ART for at least 2 years, contrary to the current study which had no time limit when ART was initiated. Also, in the study by Peck *et al.* (2014) the blood sample for CD4+cell count, was taken on the same day as the measurement of first BP (Peck *et al.*, 2014). But, in the current study, CD4+cell count was obtained from patient's records with a focus to the CD+ cell count which was taken and measured in a period of not more than the past 6 months counting from the day of recruitment.

Conclusion and recommendations

In conclusion the prevalence of hypertension in HIV patients on ART was 29.3% and it was significantly and positively associated with increasing age, obesity, and non-protease inhibitors. Both of duration since HIV diagnosis and current CD4+cell count was found not associated with increased odds of having hypertension.

Derived from the outcome of the study, we recommend the following:

(i)   Routine screening and monitoring of blood pressure in HIV patients is required when attending HIV outpatient clinics.

(ii) There should be the inclusion of lifestyle modification awareness programs into existing outpatient HIV clinics in Tanzania.

(iii) Future prospective studies are recommended to investigate the incidence of hypertension and its association with HIV related factors.

Abbreviations
ART, antiretroviral therapy, BMI, body mass index, cART, combination antiretroviral therapy, CTC, care and treatment clinic.

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