

# Hypertension, cardiovascular risk factors and antihypertensive medication utilisation among HIV-infected individuals in Rakai, Uganda

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## Abstract

**OBJECTIVES** To assess the prevalence of hypertension, elevated blood pressure and cardiovascular risk factors among HIV-positive individuals in rural Rakai District, Uganda.

**METHODS** We assessed 426 HIV-positive individuals in Rakai, Uganda from 2007 to 2010. Prevalence of hypertension and elevated blood pressure assessed by clinical measurement was compared to clinician-recorded hypertension in case report forms. Multiple logistic regression and z-tests were used to examine the association of hypertension and elevated blood pressure with age, sex, body mass index (BMI), CD4 cell count and antiretroviral treatment (ART) use. For individuals on antihypertensives, medication utilisation was reviewed.

**RESULTS** The prevalence of hypertension (two elevated blood pressure readings at different time points) was 8.0% (95% CI: 5.4–10.6%), and that of elevated blood pressure (one elevated blood pressure reading) was 26.3% (95% CI: 22.1–30.5%). Age  $\geq 50$  years and higher BMI were positively associated with elevated blood pressure. ART use, time on ART and CD4 cell count were not associated with hypertension. Eighty-three percent of subjects diagnosed with hypertension were on antihypertensive medications, most commonly beta-blockers and calcium channel blockers.

**CONCLUSIONS** Hypertension is common among HIV-positive individuals in rural Uganda.

**keywords** hypertension prevalence, treatment, HIV, Rakai, Uganda

## Introduction

Most mortality in sub-Saharan Africa (SSA) is currently due to communicable diseases, but WHO estimates that by 2030 non-communicable diseases (NCDs) will be the most common causes of death (Alwan *et al.* 2010; Jamison *et al.* 2013). As NCDs rise to account for 46% of all deaths by 2030, the SSA region will face a 64% increase in deaths due to NCDs – the largest per cent increase of all regions (Nikolic *et al.* 2011).

Many studies have documented the emerging burden of NCDs in rural and urban SSA, including rates of and risk factors for hypertension, stroke, diabetes mellitus and ischemic heart disease (BeLue *et al.* 2009; Hall *et al.* 2011; Chin 2012; Kolo *et al.* 2012; Shavadia *et al.* 2012;

Dewhurst *et al.* 2013; Kandala *et al.* 2013; Ntsekhe & Damasceno 2013; Ojji *et al.* 2013; Onen 2013; Onwuchekwa *et al.* 2013; Peck *et al.* 2013; Pires *et al.* 2013). Recent meta-analyses document the overall prevalence of hypertension in the general population to be 16.2% (Twagirumukiza *et al.* 2011; Ogah & Rayner 2013). In Uganda, cross-sectional surveys defined hypertension as one elevated blood pressure reading and found a prevalence of 27.2% in a mostly rural population (Musinguzi & Nuwaha 2013) and 22% in a strictly rural population (Maher *et al.* 2011).

Among HIV-positive patients, as access to antiretroviral treatment (ART) expands in SSA, people living with HIV will develop comorbid chronic conditions such as hypertension. Further, hypertension incidence is expected to rise

L. D. Sander *et al.* **Hypertension and HIV in Rural Uganda**

due to migration to urban areas and associated changes in lifestyle factors, including diet and physical activity (Yusuf *et al.* 2001; Addo *et al.* 2007; BeLue *et al.* 2009; Musinguzi & Nuwaha 2013). HIV and ART may also result in physiological changes, such as inflammation or metabolic syndrome, which may contribute to hypertension and cardiovascular mortality, although studies have reported conflicting results (Gazzaruso *et al.* 2003; Jericó *et al.* 2005; Seaberg *et al.* 2005; Triant *et al.* 2007).

The objectives of this study were to determine the prevalence of and risk factors for hypertension and elevated blood pressure and to assess hypertension treatment and antihypertensive medication utilisation among HIV-infected persons in rural Uganda.

## Methods

### Study population

The Rakai Health Sciences Programme (RHSP) conducts the Rakai Community Cohort Study (RCCS) and provides antiretroviral therapy (ART) and HIV care throughout rural Rakai District, Uganda.

This analysis uses data from a randomised trial of HIV-1 and HSV-2 coinfecting individuals, conducted between 2007 and 2010 (Reynolds *et al.* 2012). Pre-ART subjects were identified from RHSP clinics and affiliated HIV care programmes. Approximately one-third of participants were part of RCCS, and the remaining participants were from the general Rakai population. Inclusion criteria were age 18 years or older, seropositivity for HIV-1 and HSV-2 and a CD4 cell count between 300 and 400 cells/mm<sup>3</sup>. Individuals with AIDS-defining illnesses were excluded. A full description of the methodology has been previously reported (Reynolds *et al.* 2012). Individuals were randomised to receive 400 mg acyclovir twice daily *vs.* placebo for 24 months. ART was initiated if the CD4 cell count declined below 250 cells/mm<sup>3</sup> or WHO stage 4 disease. Participants were followed monthly for up to 42 months and were censored when they started ART.

The study was approved by the Uganda Virus Research Institute's Science and Ethics Committee, the Uganda National Council for Science and Technology and the US National Institutes of Health, National Institute of Allergy and Infectious Diseases Intramural Institutional Review Board.

### Measurements and statistical analysis

At every 6-month study visit, blood pressure, height, weight and CD4 count were measured via clinical

examination. Clinical endpoints of interest included hypertension and elevated blood pressure. Hypertension was defined as blood pressure of  $\geq 140$  mmHg systolic or  $\geq 90$  mmHg diastolic blood pressure on two or more visits per the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) recommendations (Pickering *et al.* 2005). Elevated blood pressure was used as an endpoint to compare to cross-sectional studies that only document one elevated blood pressure reading and was defined as having one (or more) blood pressure readings  $\geq 140$  mmHg systolic or  $\geq 90$  mmHg diastolic blood pressure. Elevated blood pressure was inclusive of those who were hypertensive. Body mass index (BMI) was defined as weight in kilograms divided by height in metres squared and categorised according to WHO criteria: BMI  $< 18.5$  is underweight, BMI 18.5–24.9 is normal, BMI 25.0–29.9 is overweight, and BMI  $\geq 30.0$  is obese (World Health Organization 1995).

In addition, clinicians documented a diagnosis of hypertension on study case report forms if the systolic blood pressure was  $\geq 140$  mmHg and/or the diastolic blood pressure was  $\geq 90$  mmHg. This is termed 'clinician-recorded hypertension'.

The prevalence of hypertension and elevated blood pressure was calculated from clinical examination measurements taken at study visits and compared to clinician-recorded hypertension using  $z$ -tests. The prevalence of hypertension and elevated blood pressure was compared between sexes, two age categories ( $< 50$  and  $\geq 50$  years), four categories of BMI (underweight, normal, overweight, obese) and among three categories of CD4 count ( $< 200$ , 200–350 and  $\geq 350$  cells/mm<sup>3</sup>). Multiple logistic regression was used to model the effects of age, gender, BMI and CD4 cell count on hypertension and elevated blood pressure. Subjects were also stratified by ART use, and the prevalence of hypertension was compared using a  $z$ -test. The association between time on ART and hypertension was estimated using logistic regression. For subjects on antihypertensive medications, utilisation was reviewed and categorised according to drug class.

## Results

### Prevalence of and risk factors for hypertension and elevated blood pressure

Of the 1006 subjects screened for the study, 11.9% ( $n = 107$ ) had elevated blood pressure at baseline. The majority of subjects were ineligible because they did not meet CD4 cell count criteria. Among the 426 enrolled

participants, mean follow-up time was 18.4 months, with range 6–42 months. Characteristics of the 426 subjects enrolled into the trial are presented in Table 1.

All subjects had their blood pressure measured on at least two or more occasions. The prevalence of hypertension during the study period was 8.0% (95% CI: 5.4, 10.6%), and the prevalence of elevated blood pressure was 26.3% (95% CI: 22.1, 30.5%). In contrast, the prevalence of clinician-recorded hypertension on study case report forms was 4.2% ( $n = 18$ ) of study subjects ( $P < 0.05$  for both comparisons).

Table 2 shows the prevalence of hypertension and elevated blood pressure by gender and age. The prevalence of hypertension among women was 7.6% (23 of 302), and among men it was 4.6% (11 of 124,  $P = 0.67$ ). For elevated blood pressure, the prevalence was 25.2% (76 of 302) for women and 29% (36 of 124) for men ( $P = 0.36$ ). Stratified by age, women <50 years had a lower prevalence of hypertension and elevated blood pressure ( $P < 0.05$ ). For males, the prevalence of hypertension or elevated blood pressure was not statistically different between age categories, although there was a trend in this direction ( $P = 0.19$  and  $P = 0.48$ , respectively).

There was a positive relationship between hypertension and elevated blood pressure with elevated BMI (Table 3). While the prevalence of hypertension and elevated blood pressure was similar among underweight and normal weight subjects, there was a significant difference in hypertension between normal weight individuals and those who were overweight or obese ( $P < 0.05$ ), and in elevated blood pressure between normal weight individuals and those who were obese ( $P < 0.05$ ).

There was no association between hypertension or elevated blood pressure and CD4 cell count. For subjects with CD4 <200 cells/mm<sup>3</sup>, the prevalence of hypertension was 10% (one of 10), 6.8% (14 of 206) for subjects

with a CD4 cell count between 200 and 350 cells/mm<sup>3</sup> and 9.0% (19 of 210) for subjects with a CD4 cell count >350 cells/mm<sup>3</sup>. Similarly, the prevalence of elevated blood pressure for subjects with CD4 <200 cells/mm<sup>3</sup> was 20% (two of 10), compared to 28.6% (59 of 206) for subjects with a CD4 cell count between 200 and 350 cells/mm<sup>3</sup> and 24.2% (51 of 210) for subjects with a CD4 cell count >350 cells/mm<sup>3</sup>.

In a multiple logistic regression model with predictors of age, sex, BMI and CD4 cell count, the odds of hypertension were increased with each single year increment of age (aOR = 1.08, 95% CI: 1.04, 1.12) and each incremental increase of BMI (aOR = 1.15, 95% CI: 1.05, 1.26). In a similarly fit model for elevated blood pressure, odds of elevated blood pressure were increased with each incremental year of age (aOR = 1.04, 95% CI: 1.02, 1.06) and each incremental increase of BMI (aOR = 1.11, 95% CI: 1.04, 1.18).

The prevalence of hypertension for subjects on ART was 8.2% ( $n = 14$  of 170), and for those not on ART the prevalence was 7.8% (20 of 256,  $P = 0.87$ ).

#### Hypertension treatment and antihypertensive medication utilisation

Eighty-three per cent (15 of 18) of study subjects diagnosed with hypertension were documented to be on indicated medications. The most frequent medication class prescribed was beta-blockers (39.7%, e.g. atenolol, propranolol), followed by calcium channel blockers (e.g. nifedipine), 37.2%; loop diuretics (e.g. furosemide), 13.2%; thiazide diuretics (e.g. bendrofluazide, bendroflumethiazide), 9.2%; then potassium-sparing diuretics (e.g. spironolactone) and angiotensin-converting-enzyme inhibitors (ACEI) (e.g. captopril), 0.3% each.

#### Discussion

The overall prevalence of hypertension among rural HIV-positive individuals was 8.0%. This prevalence is consistent with rates reported from rural and urban HIV-positive subjects in Kenya (8.8%) and is lower than rates in urban populations of Uganda (15.1% and 27.9%) (Semeere *et al.* 2014; Bloomfield *et al.* 2011; Mateen *et al.* 2013). Few studies have compared rates of hypertension in HIV-positive and HIV-negative populations in SSA, and current comparisons are limited by the lack of a suitable comparison group (Bloomfield *et al.* 2014). Of note, meta-analyses have documented the overall prevalence of hypertension in HIV-negative populations of SSA to be 16.2% (Twagirumukiza *et al.* 2011; Ogah & Rayner 2013). The lower hypertension prevalence in this population of

**Table 1** Descriptive characteristics of 426 study participants

	Women $n = 302$ (71%) Median (IQR)	Men $n = 124$ (29%) Median (IQR)
Age (years)	37.7 (30.5, 43.8)	42.4 (35.3, 47.2)
Systolic blood pressure (mmHg)	110.6 (93.3, 140)	113.6 (109.3, 116.3)
Diastolic blood pressure (mmHg)	71.7 (68.0, 75.0)	73.1 (69.0, 77.2)
Body mass index (kg/m <sup>2</sup> )	23.0 (16.1, 34.6)	20.8 (19.5, 22.0)
CD4 (count/mm <sup>3</sup> )	364.6 (301.3, 408.8)	347.0 (298.8, 390.6)

IQR, interquartile range.

**Table 2** Prevalence of hypertension and elevated blood pressure by age and gender during study period

	Females			Males		
	<50	≥50	Total	<50	≥50	Total
Number of subjects with hypertension/total subjects	14/270	9/32	23/302	7/98	4/26	11/124
Prevalence of hypertension, %	5.2	28.1	7.6	7.1	15.3	4.6
Number of subjects with elevated blood pressure/total subjects	62/270	14/32	76/302	27/98	9/26	36/124
Prevalence of elevated blood pressure at study visits, %	23.0	43.8	25.2	27.6	34.6	29.0

**Table 3** Prevalence of hypertension and elevated blood pressure by body mass index (BMI) during study period

	Under-weight (BMI < 18.5)	Normal (18.5 ≤ BMI < 25)	Overweight (25 ≤ BMI < 30)	Obese (BMI ≥ 30)
	Number of subjects with hypertension/total subjects	3/31	19/330	8/46
Prevalence of hypertension, %	9.7	5.8	17.4	21.1
Number of subjects with elevated blood pressure/total subjects	8/31	79/330	14/46	11/19
Prevalence of elevated blood pressure, %	25.8	23.9	30.4	57.9

HIV-positive individuals compared to urban Ugandans, and the general population may be due to differences in distribution of major cardiovascular risk factors such as age, sex, BMI and dietary and physical activity risk factors in addition to the effects of HIV (BeLue *et al.* 2009). Further studies that account for demographic and behavioural factors are needed to understand the relationship between hypertension and HIV.

The prevalence of elevated blood pressure in this study was 26.3%. This is significantly higher than in the RCCS population, which has a prevalence of elevated blood pressure of 9.7% among 14 575 HIV-negative individuals and 8.5% among 3972 HIV-positive individuals (Sander *et al.* 2014). This discrepancy is likely due to a younger RCCS population (mean age = 28.9 years) compared to the study population. This study's prevalence of high blood pressure is similar to cross-sectional studies based on one elevated blood pressure reading in HIV-negative Ugandan populations (range 22.5–27.2%) (Maher *et al.* 2011; Musinguzi & Nuwaha 2013).

While the prevalence of elevated blood pressure was 26.3%, only 4.2% of subjects were noted to have clinician-recorded hypertension on case report forms. The difference implies there are missed opportunities for recognition of elevated blood pressure and supports literature that documents low rates of hypertension awareness, treatment and control in SSA (Addo *et al.* 2007). Incorporating chronic disease management training into regular continuing medical education activities is important for providers taking care of populations at risk.

As consistent with prior literature, older individuals ≥50 years have higher blood pressure (Mateen *et al.* 2013). Gender was not found to be a significant risk

factor for high blood pressure or hypertension in this study, likely due to lack of power to detect a gender difference. There was a positive association between BMI and hypertension consistent with other studies (Bergersen *et al.* 2003; Bloomfield *et al.* 2011). While other studies found a positive relationship between CD4 cell count and hypertension (likely mediated by BMI) (Bloomfield *et al.* 2011; Mateen *et al.* 2013), this study was underpowered to detect such an association given the limited range of CD4 cell count criteria for study enrolment. There was no association between ART use or duration of ART use and hypertension.

Of those recognised as hypertensive in this study, 83.3% were on antihypertensive medications. According to European AIDS Clinical Society guidelines, thiazide diuretics and ACEI should be first-line for antihypertensive treatment among HIV-positive patients, while beta-blockers, vasodilating agents and calcium channel blockers may all be used (Lundgren *et al.* 2008). However, beta-blockers and calcium channel blockers were more commonly used than thiazides and ACEI.

This study has several limitations. This is a secondary analysis of a randomised trial designed for other purposes and may be underpowered for detection of hypertension or elevated blood pressure. Differential follow-up time may have resulted in misclassification bias due to subjects having an unequal number of blood pressure measurements for a diagnosis of hypertension. It was also not possible to evaluate hypertension control. Behavioural risk factors for hypertension such as smoking status, alcohol, diet and physical activity and other treatment modalities for hypertension (diet and exercise) were not assessed.

Hypertension is the first risk factor to appear during the epidemiologic transition from communicable to NCDs, is easily and cheaply diagnosed and is a logical target for addressing NCDs in SSA (Boulware *et al.* 2001; Nwankwo *et al.* 2013).

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L. D. Sander *et al.* **Hypertension and HIV in Rural Uganda**

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