Association between HIV Status and Hypertension: A Prospective Cohort Study in Sub-Saharan Africa

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LAYMAN'S SUMMARY

In South Africa, 1 in 5 people are infected with HIV, a virus that attacks your body's immune system. Antiretroviral therapy (ART) is the medication used to treat HIV and has been very successful at improving the life expectancy for people with this virus. As people infected with HIV in South Arica are living longer, they are now at greater risk of other age-related chronic diseases. Heart disease and high blood pressure are of particular concern. They affect higher percentages of people living in countries with a lower-income such as South Africa, compared to people in high-income countries. The relationship between HIV and ART and high blood pressure is still unclear. Research from high-income countries shows people infected with HIV are at greater risk of high blood pressure, while studies from lower income countries show the opposite. So far, past research in Southern Africa has only looked at data from one point in time. This study is one of the first to analyse data across multiple years. This will show how a more accurate view of how blood pressure is affected by HIV and ART for people in South Africa.

We collected social, lifestyle and biological data from 1364 participants over 3 years, where 40% were infected with HIV, and 56% were female. We used statistical techniques which take into account different factors that affect blood pressure, such as a person's height, weight and age. Results from our statistical analysis showed that over time, people in South Africa who are infected with HIV and are taking ART, have a lower blood pressure than people who are not infected with HIV. This knowledge can be used to improve healthcare services in South Africa so people with high blood pressure can receive better support and access to blood pressure-lowering medications.

ABSTRACT

BACKGROUND: For people living with HIV in sub-Saharan Africa, antiretroviral therapy (ART) improved life expectancy but resulted in a concomitant increased risk of age-related cardiovascular disease (CVD) multimorbidity. So far, studies examining the relationship between hypertension and HIV and ART status are cross-sectional and lack longitudinal associations.

METHODS: A longitudinal analysis was performed on data from the Ndlovu Cohort Study, South Africa, comparing data from HIV-positive and HIV-negative individuals collected annually across a 3-year follow-up period. Linear mixed models were used to estimate trends in systolic and diastolic blood pressure by sex over time according to HIV and ART status.

RESULTS: Data was analysed from 1364 participants with a median age of 39 years (SD ± 12.8); 557 (40.8%) were HIV-positive and 764 (56%) were female. A total of 432 HIV-infected individuals were taking ART medication, of whom 78.8% measured an undetectable viral load of <50 cp/mL. The baseline hypertension prevalence (≥140/≥90 mmHg) was 20.4% in HIV-negative participants and 10.2% in HIV-positive participants on ART, which increased to 38.7% and 26.6% respectively after 36-months of follow-up. After multivariable adjustment, use of ART medication, but not HIV status, was associated with an 8.41 mmHg lower systolic blood pressure [*P*=≤0.001]. Sex-stratified analysis showed classic CVD risk factors were a specific concern for HIV-positive males.

CONCLUSIONS: South Africa is faced with a high overall burden of uncontrolled hypertension. There is a need for population-level prevention of factors associated with hypertension and CVD risk, with emphasis on improving health-seeking behaviours in men.

KEY WORDS: Anti-retroviral therapy; blood pressure; HIV; hypertension; sub-Saharan Africa

INTRODUCTION

The global HIV epidemic continues to disproportionately affect Sub-Saharan Africa (SSA), a region home to 67% of people living with HIV (PLWH) worldwide (1,2). South Africa remains at the epicentre of the HIV crisis, with a HIV prevalence of 19.1% reported in the adult general population (15-49 years) in 2020 (3). Despite a continued reduction in the number of new HIV infections, the increasingly high prevalence of PLWH can be attributed to a greater life expectancy afforded by successful implementation and scale-up of the world's largest public-sector antiretroviral treatment (ART) programme (4). This expansion in the HIV care continuum meant South Africa achieved 2 of the 3 UNAIDS 90-90-90 targets, whereby 92% of PLWH were aware of their HIV status, of which 75% were accessing ART, and 92% of those were virally suppressed by the 2020 deadline (5). The result of this increased lifespan has meant PLWH now face a greater risk of age-related non-communicable diseases (NCDs) (6).

In South Africa, cardiovascular disease (CVD) represents the highest age-standardised death rate of all NCDs (7). The prevalence of individuals affected by high blood pressure (BP) has risen disproportionately in SSA in recent years, with 46% of adults aged 25 or over classified as hypertensive compared to 35% in high-income countries (HIC)(8). As a result, the 2015 World Heart Federation (WHF) Roadmap on Hypertension has been adapted by the Pan-African Society of Cardiology (PASCAR) for more tailored national antihypertensive guidelines and community programmes within the African region (9). Here, hypertension control has been prioritised by the PASCAR Taskforce using a 10-point action plan with the aim to achieve 25% control by 2025 (10). However, hypertension and HIV comorbidity pose a more serious public health concern, necessitating long-term sustained healthcare engagement. Patients require more complex treatment regimes and are thus more susceptible to adverse drug effects and interactions, and treatment fatigue, which can undermine adherence. South Africa's Integrated Chronic Diseases Management (ICDM) model, introduced in 2011, is based on a chronic care model designed for HICs. It aims to provide an integrated healthcare platform for PLWH

with NCD co-morbidities via existing primary healthcare (PHC) facilities (11). However, studies evaluating the efficiency of the ICDM model, document training and resource constraints, which critically undermine the quality of care delivered (12,13). Our research agenda would help to address the emerging hypertensive crisis by guiding the development of a more tailored ICDM model bespoke to rural areas in SSA, for higher quality, holistic care within PHC facilities for PLWH (12,14,15).

So far, studies which investigate the association between HIV status and high BP in HICs compared to LMICs give contradicting results (16). A recent global meta-analysis of 59 cross-sectional studies examining hypertension risk by HIV status revealed significantly lower pooled risk ratios for studies focused in African regions compared to European and North American studies (17). Longitudinal studies looking at the role of HIV, and specifically the role of ART in the South African region are lacking. Research surrounding the pathophysiological mechanisms associated with HIV infection is in line with the epidemiological relationship seen in HICs. Chronic inflammation, lipodystrophy and endothelial dysfunction attributed to HIV viral infection are known mechanisms for hypertension (18). However, differential antiretroviral (ARV) treatments and population demographics found globally are thought to contribute to the observed inconsistencies in hypertensive risk for PLWH (19–22).

Access to ARVs in poor-resource settings such as southern Africa has been determined by trade-offs between costs and side effects (23). From 2018, updates in WHO guidelines for ARV regimens recommend more potent and better tolerated dolutegravir-based first and second-line treatments (24,25). However inequitable pricing has meant older efavirenz-based regimes continue to dominate as the most commonly used ARV treatment in SSA (26,27). This has impacted the generalisability of current studies from HICs examining the role of ART on hypertension. Differences in the demographics of PLWH in HICs and SSA also preclude the generalisation of existing study results. Key populations such as female sex workers, men who have sex with men, people who inject drugs and transgender women form the vast majority of PLWH in HICs where overall HIV prevalence is low.

In SSA's higher prevalence setting, these key populations represent a significantly lower proportion of HIV-infected individuals (3). This could explain the differences in classical cardiovascular and hypertensive risk factors, which are lower in PLWH compared to the general population in SA, but vice versa in HICs (28–33).

A thorough comparison of the changes in BP of HIV and non-HIV-infected individuals in SSA over time is critical in helping to develop and tailor existing public health policies to combat HIV-NCD-related comorbidity in poor-resource settings (34). This study aims to assess the role of HIV status and ART medication on changes in BP over a 36-month period in a rural SSA population and investigate the determinants of this change.

METHODS

STUDY DESIGN AND STUDY POPULATION

This study is a longitudinal analysis of the Ndlovu Cohort Study (NCS). The NCS is a prospective cohort study based in the Moutse area, Limpopo Province, South Africa, and was established to explore the relationship between CVD and ART and HIV status in a rural African area. A detailed description of study design and methods have been published previously (35). To summarise, a total of 1927 participants were recruited between November 2014 and August 2017, of which 887 (46%) were HIV-positive and 1056 (55%) were female. Participant enrolment took place through local events, community campaigns, in shopping areas and at the Ndlovu Medical Centre (NMC), a large rural HIV clinic contracted by the South African Department of Health. Inclusion criteria detailed: age ≥18 years, able to provide informed written consent and commitment to long-term follow-up. Ethical approval for the study was granted by the Human Research Ethics Committee at the University of Pretoria, Pretoria, South Africa, and the Limpopo Department of Health Ethics Committee.

MEASUREMENTS AND DEFINITIONS

At participant intake, information regarding age, gender, demographics, socioeconomic status, medical history and all chronic medication use was been collected via standardised questionnaires. Cardiovascular risk factors, smoking and alcohol use were assessed using a modified version of the WHO STEPwise approach to NCD risk factor surveillance (STEPS) instrument (36). Data on physical activity was evaluated using the International Physical Activity Questionnaire (IPAQ) in metabolic equivalent of task (MET) units, and defined as MET-min/week, categorised into low, moderate and high (37). Employment and income data were collected using the National Income Dynamics Study [NIDS] Wave 3 2012 Adults Questionnaire (38). Monthly income per person was categorised according to the lower and upper national poverty lines defined by Statistics of South Africa as 648 and 992 South African Rands (ZAR) respectively (39). Anthropometric measurements including height, weight and waist and hip circumference were obtained via physical examination. Participants were tested for

HIV upon enrolment unless they had documentation of a previous positive HIV test or proof of being on ART. Testing was compliant with South African National Department of Health guidelines (40).

Three systolic and diastolic BP measurements were collected using a sphygmomanometric device following 5 minutes of rest in the seated position. The device was applied to both arms, and measurements were repeated on the arm with the highest values. The average of the second and third measurements for both systolic and diastolic BP were used for the analysis. Elevated BP was regarded as an average systolic and diastolic BP between 120/80 mmHg and 140/90 mmHg. Participants were classified as hypertensive if they had a measured or imputed systolic BP of ≥140 mmHg or a diastolic BP ≥90 mmHg or if they were taking anti-hypertensive medication, or been informed they were hypertensive by a medical professional. Blood samples were drawn and analysed to obtain a complete non-fasting lipid panel and random glucose and HbA1c levels. From this, diabetes mellitus was termed as random glucose >11mmol/L, or HbA1c >6.4mmol/L or use of glucose-lowering medications. In cases of HIV infection, blood samples were also used to measure CD4+ cell count and viral load. All biological tests were analysed by an accredited laboratory (TogaLabs, South Africa).

Follow-up information was collected every 12 months, on the month each participant had been initially recruited. Participants were invited to the research site for a new interview and physical examination, where sociodemographic, anthropometric and BP information was recollected. HIV and ART status was reassessed by self-report and complemented by data from the electronic HIV registry TIER.net. Three instances of discrepancy were identified due to typing error and patient non-disclosure with the nurse and manually corrected with TIER.Net data preferred. TIER.Net is an integrated national electronic database using standardised clinical records to monitor HIV and tuberculosis treatments (41,42).

STATISTICAL ANALYSIS

Study characteristics were reported as mean (SD) or median (interquartile range) for continuous data, or count (percentage) for categorical data. The mean of the imputed values for variables of interest were included in data summarising study participant characteristics. At baseline, participants were divided into 4 groups: a) HIV negative b) HIV-positive ART-naïve c) HIV-positive first-line medication and d) HIV-positive second-line medication. For the analysis, participants on first and second-line medication were combined into "HIV-positive on ART" due to the small number of participants on second-line ART and high proportion of missing BP data. Differences in categorical and continuous demographics between groups at baseline were assessed using a Chi-square test and a t-test and Mann-Whitney U test respectively. Trends in BP change over time for baseline, 24 months and 36 months for the observed data were analysed using a linear mixed effects model (estimated with restricted maximum likelihood), with systolic and diastolic BP modelled separately. Participants were first grouped according to HIV status only, using HIV-negative participants as the reference group. A priori knowledge was used to identify potential risk factors for hypertension, and a directed acyclic graph (DAG) developed to identify potential confounders (**Figure 1**). A DAG-informed stepwise backward variable selection approach was then applied using the Akaike information criterion and a p-value threshold of 0.5. Time, age and sex were specified as fixed effects in model 1, and additional variables: BMI, consumption of alcohol in the last 30 days, use of BP medication, and the interaction between time and HIV status were included in the second model. Time was modelled as a categorical variable for baseline, 24 months and 36 months, using baseline as the reference. In both models, a random intercept model with uncorrelated residuals was applied. Steps were repeated in a final model to determine the association between ART status and BP change, and further accounting for sex.

Of the participants included in the study, a total of 34.9% BP measurements were regarded as missing due to the use of a non-validated wrist device between 2016 and 2017. The distribution of missing data meant BP measurements at 12-month follow-up were majorly affected (97.2%) and thus

were excluded entirely from the analysis. For baseline, 24 months and 36 months, 39.0%, 61.4% and 2.3% of BP data was regarded missing respectively and assumed to be missing completely at random. Of all other variables included in the analysis, missing data was <1.5%.

Multiple imputation was performed using a two-stage approach owing to the high percentage of missing data at 24 months follow-up to reduce bias estimates and over-confident inferences (43,44). As the observed mean BP measurements were right skewed, the nested imputation was performed using a fully conditional specification approach as this is more robust to violations of normality. Continuous variables were modelled using predictive mean matching, limiting imputed values to within the range of observed values (45). For categorical variables, a (multinomial) logistic regression model was used. Longitudinal data was arranged in wide format, with repeated measures assumed as distinct variables and classical cross-sectional imputation methods applied (46). Study characteristics were reported by sex prior to multiple imputation. Multiple imputation was first performed for baseline and 36 months follow-up only, using all valid measurements for systolic and diastolic BP, age, sex, HIV status, ART status, education, employment, smoking, alcohol, physical activity, waist circumference, pulse rate, viral load, diabetes, use of antihypertensives and family history of CVD at baseline and 36 months. Measurements for ART duration, BMI and CD4+ cell count were excluded from the first-stage imputation model due to high co-linearity identified by univariate analyses[i]. A total of 20 imputed datasets were generated from the first round of imputation due to computational limitations. All missing data for 24 months follow-up, and any missing data for BMI, ART duration and CD4+ cell count across the three time points were imputed in the second stage of imputation. Imputed values were then treated as fixed values, with predictors included in the first-stage imputation model repeated in the second-stage model for baseline, 24 months and 36 months, in addition to BMI, ART duration and CD4+ cell count. The number of imputations in the second-stage was set to one, generating an overall total of 20 imputed datasets, and mitigating a nested analysis of variance paradigm (47). The complete imputed data was then rearranged into long format prior to analysis. Plausibility of imputations were assessed graphically through density plots to confirm there

were no discrepancies between the distribution of observed and imputed data (**Supplementary Figure 1**). Each of the 20 stacked imputed datasets were analysed separately, with parameter estimates per model combined according to Rubin's formula. Multiple imputation was performed using SAS Studio (SAS Institute Inc), and analysis and pooling using RStudio (v4.1.0).

A sensitivity analysis was conducted to confirm the robustness of the linear mixed effects model to the missing outcome data, with the imputed datasets used to fit the final analysis models. Regression coefficients for the mixed model analyses with and without multiple imputations were compared to ensure no substantial differences. Data cleaning and management were performed using IBM SPSS Statistics version 28.0, and all other analyses, except the generation of the 20 multiple imputed datasets were conducted using RStudio (v4.1.0).

ETHICAL CONSIDERATIONS

Ethics approval for the NCS was granted by the Human Research Ethics Committee at the University of Pretoria, Pretoria, South Africa. Informed written consent was obtained for all subjects before study participation.

RESULTS

1927 patients were recruited in the NCS. 540 participants were excluded where information was only available for baseline and 12 months follow-up, and a further 21 female participants due to pregnancy at either baseline, 24 or 36-month follow-up, and 2 participants due to inconsistent data. For the purpose of this study, a total of 1364 participants were included (**Figure 2**). The mean age of the study population was 39.0 years (SD ± 12.8) and 764 (56%) were female (**Table 1**). Men were nearly 12 times more likely to smoke than women and 6 times more likely to have consumed alcohol in the past 30 days. Of the participants with missing BP information, 42% were female at baseline, 63% at 24 months follow-up and 54% at 36 months. A total of 54% were HIV-positive at baseline, 37% at 24 months and

43% at 36 months follow-up. Mean age, BMI and waist circumference were comparable to that of the total study population across all follow-up periods. Loss to follow-up was 9.5% at 24 months and 13.8% at 36 months. Of those taking ART medication, HIV was well controlled with 78.8% measuring a viral load of <50cp/mL (**Table 2**).

Women had a significantly lower systolic and diastolic BP (115.4 mmHg versus 120.2 mmHg *P*=≤0.001 and 74.5 mmHg versus 75.1 mmHg *P*=0.016) at baseline compared to male participants (**Supplementary Figure 2**). Baseline systolic BP for HIV-negative participants was significantly higher than for HIV-positive participants (119.1 mmHg versus 115.1 mmHg *P*=≤0.001) but there was no difference in diastolic BP (74.8 mmHg versus 74.6 mmHg) (**Figure 3**). A total of 226 participants (16.6%) were classified as hypertensive at baseline, of whom 75 (33%) were taking anti-hypertensive medication. For all groups, regardless of sex or HIV status, BP increased over the period of the study. At baseline, 165 (20.4%) HIV-negative participants were classified as hypertensive, and 198 (24.5%) had an elevated BP, which increased to 226 (38.7%) and 227 (33.0%) respectively at 36 months follow-up (**Figure 4**). Of the HIV-positive participants on ART, 44 (10.2%) were classified as hypertensive at baseline, rising to 101 (26.6%) at 36 months follow-up.

ASSOCIATION BETWEEN HIV STATUS AND BLOOD PRESSURE

There was a significant increase in both mean systolic and mean diastolic BP for HIV-positive (*P*=≤0.001) and HIV-negative (*P*=≤0.001) participants between baseline and 36 months follow-up (**Table 3**). After adjustment for age and sex, HIV infection was associated with an 8.9 mmHg lower systolic BP (95% confidence interval [CI], 10.8-6.9) and 3.3 mmHg lower diastolic BP (95% CI, 4.5-2.1). Following further adjustment for other potential confounders, HIV infection was still associated with a 4.3 mmHg lower systolic BP (95% CI, 6.7-1.8), however, for diastolic BP the association was attenuated. Older age and higher BMI was associated with an increase in systolic and diastolic BP (*P*=≤0.001). Waist circumference was excluded due to high multicollinearity with BMI, with BMI taking

preference due to a stronger association (**Supplementary Table 2**). Use of BP medication was associated with higher systolic (*P*=0.015) and diastolic BP (*P*=0.046). The effect of study duration on mean systolic BP was shown to differ between HIV-positive and HIV-negative groups, with those infected with HIV having a 3.8 mmHg lower systolic BP (95% CI, 6.2-1.5) at 36 months compared to HIV-negative individuals. Smoking, diabetes education and employment were not associated with changes in BP.

ASSOCIATION BETWEEN ART STATUS AND BLOOD PRESSURE

The trends in mean BP by ART status over time are presented in **Figure 5**. Mean systolic and diastolic BP significantly increased across the 36 months follow-up period, and was higher in HIV-positive participants on ART compared to HIV-negative participants following adjustment for age and sex (SBP, β=-10.51 [*P*=≤0.001] and DBP, β=-3.96 [*P*=≤0.001]) (**Table 4**). There was no significant increase in systolic or diastolic BP for those who were HIV-positive ART-naïve compared to the HIV-negative group across the 36 months follow-up period. Following inclusion of confounders for hypertension, namely BMI, alcohol consumption in the last 30 days and use of antihypertensive medication, the association between HIV-infection and use of ART for systolic and diastolic BP remained similar and significant (β=-8.41 [*P*=≤0.001] and β=-2.71 [*P*=≤0.001] respectively). The association between mean systolic and diastolic BP and ART status was further analysed for men and women separately. For women, HIV positivity and use of ART medication were inversely associated with both systolic and diastolic BP (β=-8.65 [*P*=≤0.001] and β=-3.39 [*P*=≤0.001] respectively), whilst associations between alcohol consumption, and use of BP lowering medication and BP were attenuated. For men, HIV infection and use of ART medication was inversely related with systolic BP only (β=-7.27 [*P*=≤0.001]), alongside other CVD risk factors.

A sensitivity analysis comparing the regression coefficients and standard errors for the association of mean BP and ART status with and without multiple imputation showed similar results

(**Supplementary Table 1**). Standard errors were slightly lower in the results from the multiply imputed data, and the association of HIV infection and ART medication on systolic BP was lower in the imputed data (β=-6.07 versus β=-4.23) however overall statistical significance remained the same (*P*=≤0.001).

DISCUSSION

This study is one of the first to examine blood pressure changes between HIV-positive and HIV-negative individuals longitudinally in a rural African setting. Key findings show that use of ART medication, but not HIV-infection was inversely associated with systolic and diastolic BP over time after multivariable adjustment. Behavioural risk factors such as alcohol consumption and use of BP medication were associated with a higher systolic and diastolic BP over the 36 months follow-up specifically amongst men.

These results contrast findings from high-resource settings assessing BP in PLWH longitudinally, where HIV and use of ART medication were found to be associated with increased prevalence of hypertension compared to the general population (16,19,48). Results from the D:A:D study, a large-scale prospective cohort study, demonstrated associations between the use of ARVs and hypertension across the USA, Europe and Australia (49). Likely explanations for this difference are low numbers of participants with a detectable viral load within our study population, as viremia was well controlled with 78.9% of HIV-positive participants measuring a viral load of <50cp/mL at baseline, compared to only 38.1% in individuals from the D:A:D study. Lifestyle and socio-economic disparity are also probable contributors to the differences we see in results between SAA and resource-rich settings (50). Recent cross-sectional studies assessing the relationship between BP and HIV in African settings (51–54) including two large meta-analyses (17,20), are in line with the results of our study, reporting lower odds of high BP among PLWH. Studies assessing the relationship between BP and ART status were lacking, with even less including a sex-stratified analysis. Longitudinal studies examining HIV and hypertension in SSA are also few and give mixed results, with some reporting a lack of any

association between incident hypertension and ART status (55,56). Others, which reported an increased incidence of hypertension for PLWH on ART focussed only on HIV-positive populations and lacked a comparison with HIV-uninfected controls (57–59). Data from TIER.Net showed older fixed dose efavirenz-based regimes (1TFE) contributed the vast majority of first-line ART medication within our study population which could be a contributing factor to the differences we see in these studies.

Variation in the relationship between HIV infection and ART status and BP by sex is also in line with other research from southern Africa (51,60). The well-documented mediation effect of BMI and HIV on BP (61–63) should be considered given the differences in the prevalence of overweight and obesity in women versus men in our study, with women almost 3 times more likely to be overweight or obese compared to men. Poor male engagement with both general and HIV-specific healthcare is also well described (64–66), and could explain the sex-specific association between alcohol consumption, and use of antihypertensive medication and BP, which suggests possible low levels of adherence to BP lowering medication.

Within this study population, BMI-based measures of general obesity were found to be the strongest anthropometric predictor for increased BP over measures of central obesity. Generally, waist circumference, an indicator of visceral adiposity, systemic inflammation and a poorer metabolic profile, is accepted as a greater contributor to higher BP (61,67,68). An explanation for this difference could be the higher proportion of women within our study and the varying sex-dependent overweight and obesity profiles. BP lowering medication was unexpectedly associated with a higher systolic and diastolic BP across the 36 months follow-up. Of those who reported using anti-hypertensive medication, the mean baseline systolic BP for HIV-positive and HIV-negative participants was 138.7mmHg and 139.4mmHg respectively. This high uncontrolled BP across all study participants indicates likely poor control of BP, possibly due to low levels of adherence or limited availability to antihypertensive medication irrespective of HIV status. Poor adherence to BP medication has been found to be significantly associated with uncontrolled BP in several studies across SSA (69–71) and has

been highlighted as a major obstacle to tackling the hypertensive crisis (72). The barriers faced in antihypertensive medication adherence, namely low hypertension awareness, treatment fatigue, and adverse treatment effects mirror many of the barriers to ART adherence, however, viral suppression is conversely very high in our study population. Whilst ART medication is free and widely accessible in SSA, the availability of antihypertensive medication at PHC facilities is often intermittent, with costs borne directly to patients through out-of-pocket expenses (73,74). Accessibility and costs, coupled with the high percentage of unemployment, and high proportion of participants living below the South African poverty line (<648 ZAR per month) in our study population are likely explanations for poor hypertension control (39).

STUDY STRENGTHS AND LIMITATIONS

Major study strengths include the large sample size, inclusion of a HIV-negative control group and good representativeness of a rural South African population. Linkage of follow-up data with TIER.Net also strengthened the quality and robustness of data grouping participants as HIV-negative, HIV-positive ART naïve and HIV-positive on ART.

Some limitations should be kept in mind when interpreting the results of this study. Although assumed to be missing completely at random, the percentage of participants with invalidated BP results was high, particularly affecting data from 24 months follow-up. To assess potential bias, a sensitivity analysis was conducted where analyses were repeated using data multiply imputed via a two-stage approach. While this resulted in a slight downwards estimation in regression coefficients, significance and subsequent conclusions did not change. The mean systolic and diastolic BP for participants with multiply imputed data was slightly higher than that of the general population, however, these differences are likely attributed to a higher percentage of HIV-negative participants being associated with higher BP within this group. The high percentage of missing BP values also precluded any statements over the incident rate of hypertension within our study population.

Whilst robustness to missing data in the use of a linear mixed model was confirmed, some model assumptions were violated in regards to normality of residuals and the linearity assumption, meaning a complete absence of bias cannot be assumed. Both variable transformation and spline models were assessed to improve the regression model. Log-transformation of BP data only showed limited improvement to the normality assumption, and thus was not included in the model given the trade-off of reduced interpretability of results, and inaccuracies that arise from transforming and back-transforming parameter estimates (75). Implementation of a 3-knot natural spline model was also assessed to model any non-linear relationship between age and BP (**Supplementary Figure 5**). While this did show a significant improvement in model fit (**Supplementary Table 3**), the improvement was still very small as non-linearity stemmed only from a small number of older-aged participants, thus splines were omitted for fear of overfitting.

A case-by-case comparison of self-reported ART status from the NCS at follow-up with available data from the TIER.Net registry showed discrepancies in 10.9% of data regarding the use of first- or second-line ART regimes. This uncertainty, added to the low prevalence of second-line ART and limited variability in the specific types of ART regimes precluded any analysis looking at associations between ART lines, types of ART medication, or any HIV-related characteristics and their potential impact on BP. The follow-up period of this study was also relatively short and included only 3-time points after the exclusion of 12 months follow-up due to missing BP data. A longer follow-up period, where data would continue to be unaffected by the use of an unvalidated wrist device could provide better insights into the longitudinal association between HIV, ART medication and hypertension.

CONCLUSION

Our results show a significant increase in BP across all groups and suggest a high overall burden of uncontrolled hypertension in this rural African population. Findings suggest that the use of ART medication, as opposed to HIV-infection itself, is associated with lower systolic and diastolic BP in women, and a lower systolic BP in men. More longitudinal studies with longer follow-up periods are needed to confirm these results and to further investigate associations between specific ART regimes which may underlie the differences seen in low-and middle and high income countries with different PLWH population characteristics. This study highlights the need for the incorporation of evidence-based hypertension management into the already successful and pre-existing HIV care cascade. Specific emphasis should also be placed on improving male engagement with healthcare services, alongside other lifestyle-related non-pharmacological interventions surrounding CVD risk factors.

NONSTANDARD ABBREVIATIONS AND ACRONYMS

ART = Antiretroviral therapy, ARV = antiretrovirals, BP = blood pressure, BMI = body mass index, CVD = cardiovascular disease, DAG = directed acyclic graph, HDL-C = high-density lipoprotein-cholesterol, HIC = high-income countries, ICDM = Integrated Chronic Diseases Management, IPAQ = International Physical Activity Questionnaire, IQR = interquartile range, LMIC = low middle-income countries, MET = metabolic equivalent task, NCD = non communicable disease, NMC = Ndlovu Medical Centre, PASCAR = Pan-African Society of Cardiology, PCH = public healthcare facilities, PLWH = people living with HIV, SSA = sub-Saharan Africa , WHF = World Heart Federation, ZAR = South African Rand

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[i] Univariate analysis was performed whereby each variable was put as a dependent variable in a regression analysis and analysis of variance using all other variables as predictors. High explained variance (R^2 values close to 1) were then used as indicators of co-linearity and variables were then excluded one by one from the imputation model until warnings surrounding linear combinations of effects in the imputation model were no longer generated.