Received: 27 March 2020 | Revised: 11 May 2020 | Accepted: 16 May 2020

DOI: 10.1111/jch.13975

ORIGINAL PAPER

WILEY

Blood pressure, T cells, and mortality in people with HIV in Tanzania during the first 2 years of antiretroviral therapy

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Funding information
The study was supported by Dr Peck's NIH K01TW010281 grant, Dr Fitzgerald's NIH K24AI098627 grant, and the Weill Cornell Medicine UL1TR000457 grant.

Abstract

Cardiovascular disease is now a leading cause of mortality in people with HIV (PWH). High blood pressure is the major driver of cardiovascular disease. Despite this, little is known about blood pressure in PWH during the early years of antiretroviral therapy (ART). In this prospective cohort study in Tanzania, the authors conducted unobserved blood pressure measurements at enrollment, 3, 6, 12, 18, and 24 months in 500 PWH initiating ART and 504 HIV-uninfected adults. The authors excluded measurements taken on antihypertensive medications. Although PWH had a significantly lower blood pressure before ART initiation, they had a significantly greater increase in blood pressure during the first 2 years of ART compared to HIV-uninfected controls. Blood pressure correlates in PWH differed from HIV-uninfected controls. In PWH, lower baseline $CD4^+$ T-cell counts were associated with lower blood pressure, and greater increases in $CD4^+$ T-cell counts on ART were associated with greater increases in blood pressure, both on average and within individuals. In addition, PWH with a systolic blood pressure (SBP) <90 mm Hg at the time of ART initiation had ~30% mortality in the following 3 months due to occult infections. These patients require careful investigation for occult infections, and those with tuberculosis may benefit from corticosteroids.

1 | INTRODUCTION

People with HIV (PWH) are at a higher risk of mortality due to cardiovascular disease when compared to the general population.[1] Hypertension is a main driver of cardiovascular disease.[2] Cross-sectional studies examining the relationship between HIV and hypertension have reported inconsistent results.[3,4] Prospective studies have reported a high incidence of hypertension in PWH,[5-7] but have lacked HIV-uninfected control groups for comparison. The authors of the largest of these cohort studies recently concluded, "an HIV-negative comparison population is needed to assess the association of the HIV itself with hypertension".[5] This is especially true for the early ART period when immune reconstitution is occurring in PWH.

In a cross-sectional study, we previously conducted in Tanzania, PWH were found to have lower blood pressure than HIV-uninfected adults prior to ART initiation but higher blood pressure several years after initiation of ART.[8] We postulated that immune reconstitution may have played a role in this reversal.[7] This hypothesis is based on evidence from animal models, suggesting that changes in T-cell immunity contribute to the pathophysiology of hypertension.[9]

In this paper, we report an analysis of pre- and early ART data from our cohort investigating blood pressure in PWH and HIV-uninfected controls in Tanzania. Our objectives were as follows: (a) to investigate the pattern of blood pressure change in the first 24 months of ART, (b) to determine factors associated with blood pressure, and (c) to describe the relationship between pre-ART blood pressure and mortality in PWH.

2 | METHODS

2.1 | Study design

We conducted a prospective cohort study of PWH and HIV-uninfected adults. PWH were enrolled from public HIV clinics in the city of Mwanza, Tanzania, along with their HIV-uninfected "treatment supporters." According to Tanzanian guidelines, PWH must designate a family member or neighbor as a "treatment supporter" at the time of ART initiation who provides social and medical support. We have previously shown that treatment supporters and PWH have similar socioeconomic characteristics.[8]

2.2 | Inclusion and exclusion criteria

Inclusion criteria for HIV-uninfected adults were age 18-65 years, able and willing to be contacted by cell phone, Tanzanian citizenship, residing in Mwanza City, and able and willing to provide written informed consent. Additional inclusion criteria for PWH were no prior exposure to ART and willing to initiate ART within 1 month. Exclusion criteria for both groups were previous history of cardiovascular events, medical condition with a prognosis of <12 months, and plans to move away from Mwanza.

2.3 | Study location

All of the study participants included in this analysis were enrolled from three public outpatient HIV clinics in Mwanza, Tanzania: Bugando Medical Centre, Igoma Health Center, and Nyamagana District Hospital. The prevalence of HIV in the catchment area for these three HIV clinics is approximately 6%, which is similar to the national average. At the time of the study, these HIV clinics were providing outpatient care to over 15 000 PWH.

2.4 | Study procedures

All study participants were seen at enrollment, 3 months, 6 months, and then every 6 months thereafter. At every study visit, the study staff administered a standardized questionnaire based on the World Health Organization's STEPwise Surveillance (STEPS)[10] to evaluate risk factors for hypertension. The STEPS questionnaire has been translated into the local language (Kiswahili), has been validated in East Africa,[11] and includes questions about socioeconomic status, diet, and exercise and protocols for anthropomorphic measurements. Additional questions regarding HIV diagnosis and treatment were included. After completing the questionnaire, the study staff conducted a standardized physical examination (including weight, height, and waist circumference) according to the STEPS protocol. BMI was calculated using this height and weight.

2.5 | Blood pressure measurement

In order to minimize measurement bias, blood pressure was measured at every study visit using an OMRON HBP-1300 professional blood pressure monitor following National Health and Nutrition Examination Survey (NHANES) blood pressure procedure.[12] Participants rested for 5 minutes, sitting with back supported, legs uncrossed, and feet flat on floor. Three successive, unobserved blood pressure measurements were taken on the right arm with a 60-second interval between measurements. Average SBP/DBP was calculated using the second and third measurements. We excluded blood pressure measurements taken while participants were receiving blood pressure–lowering medications.

2.6 | Laboratory procedures

Routine point-of-care laboratory tests were performed and recorded at all study visits. $CD4^+$ T-cell counts, total lymphocyte counts, and hemoglobin levels were measured using an automated BD FACSPresto™ System (BD Biosciences). Point-of-care random blood glucose levels were measured from a sterile fingerpick (OneTouch Select, LifeScan). For any participant with a random blood glucose level ≥7 mmol/L, a fasting blood glucose measurement was obtained to confirm the diagnosis of diabetes mellitus in accordance with the guidelines of the International Diabetes Federation.[13] Anemia was categorized according to the World Health Organization definition.[14]

Additionally, blood and urine were collected at baseline. The blood samples were transported in a cooler to the laboratory of the Tanzanian National Institute for Medical Research (NIMR). Serum creatinine level was measured in the NIMR laboratory using the A25 Analyzer (Biosystems), calibrated by the creatinine Jaffé 2 method. An estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (without ethnic factor), which has been shown to be the most accurate eGFR calculation for African adults.[15] Urine albumin and creatinine were measured with the Siemens DCA Vantage Analyzer (Siemens Healthcare).

2.7 | Data analysis

Data were double-entered into OpenClinica (OpenClinica LLC) and analyzed using Stata 15 (StataCorp LLC). Outcomes variables included blood pressure and mortality, and the main confounders were age, sex, and adiposity. Continuous variables were summarized by median and interquartile range [IQR]. Categorical variables were summarized by frequency and percentage. We performed simple and multiple linear regression models to determine factors independently associated with blood pressure. We used backward selection, until we arrived at the final model with all remaining factors significant with *P*-value of <.05. Forward selection, Akaike information

criterion (AIC), and Bayesian information criterion (BIC) were also used for robustness of the final model selection. Probability of survival was estimated using the standard Kaplan-Meier (KM) method, and the multiple KM curves were compared using the log-rank test. Factors associated with mortality were assessed using Cox proportional hazard models while adjusting for other covariates. Longitudinal trend of blood pressures was analyzed using linear mixed-effects models with time and HIV fixed effects and patient-specific random effects. Tests of HIV group differences in blood pressure trends over time were assessed using the asymptotic chi-square test. All available data were included in the analysis.

2.8 | Ethics

The study was carried out in accordance with Good Clinical Practice. The study and consent forms were approved by the IRBs of Weill Cornell Medicine (Protocol 1506016328), the Tanzanian National Institute of Medical Research (Protocol NIMR/HQ/R.8c/Vol.1/1399), and Bugando Medical Centre (Protocol CREC/074/2015). All participants provided written informed consent. All PWH were provided free treatment according to the Tanzanian national guidelines.[16] For participants with hypertension, we assisted them to purchase medications for hypertension using money from a private foundation.[17]

3 | RESULTS

3.1 | Study population

Between June 2016 and August 2019, we screened 1427 people. Reasons for non-enrollment were as follows: known cardiovascular disease (125), living outside study area (79), unable/unwilling to consent (76), prior ART use (71), no phone (63), outside age range (7), and prognosis <1 year (6).

We enrolled 1000 participants (496 PWH and 504 HIV-uninfected). Four of the HIV-uninfected participants have now been infected with HIV. Since these four participants contribute observation time in both the PWH and HIV-uninfected groups, we have included these 4 in both groups, making the total number of observations 500 PWH and 504 HIV-uninfected. We analyzed data up to 2 years of follow-up for each participant. The mean follow-up time of participants was 17.3 months. At the time of analysis, 904 participants were in follow-up, 35 had died, and 61 were lost to follow-up.

3.2 | Baseline characteristics

The baseline characteristics for the 1004 PWH and HIV-uninfected participants are displayed in Table 1. The average age was similar between PWH and HIV-uninfected participants (36 [29-43] vs 35 [26.5-43] years). Two-thirds of study participants were female (68.6% vs 66.5%). The median body mass index (BMI) was 22 kg/m^2 in both groups. The median CD4$^+$ count of PWH was 413 [164-594]. Albuminuria (ACR ≥ 30 mg/g) was more common in PWH (14.2% vs 6.8%), though renal function (eGFR < 60 mL/min/1.73 m^2) was similar in both groups (10.4% vs 10.7%). Most had never had their blood pressure measured before the day of enrollment (57% vs 61%).

3.3 | Baseline blood pressures

At the time of enrollment, both SBP and DBP were significantly lower in the PWH compared to HIV-uninfected participants. The median SBP was 113.5 [104.0-124.5] mm Hg in PWH vs 123 [112.0-134.0] mm Hg in HIV-uninfected controls ($P < .001$). The median diastolic blood pressure (DBP) was 74.5 [68.0-82.0] vs 78 [71.5-85.0] mm Hg ($P = .005$).

3.4 | Factors associated with enrollment blood pressure

We examined the associations between all exposure variables in Table 1 with SBP at enrollment using univariable and multivariable linear regression models. All exposures significantly associated with higher baseline SBP are displayed in Table 2. After adjusting for confounding in multivariable linear regression models, the factors most strongly associated with higher SBP at baseline were HIV-uninfected status, higher BMI, male sex, older age, higher hemoglobin, and lower fruit consumption. After adjustment, baseline SBP remained 6.3 [4.3-8.3] mm Hg lower in PWH.

Table S1 displays the factors from Table 1 that were significantly associated with baseline DBP. After adjustment, baseline DBP remained 2.1 [0.8-4.3] mm Hg lower in PWH.

3.5 | Effect modification by HIV status

We analyzed whether exposures associated with SBP and DBP differed by HIV status using a *P*-value for interaction (Table 2 and Table S1). HIV status was a significant modifier in the relationship between CD4$^+$ T-cell count and SBP (see Figure 1A). By stratified linear regression, a statistically significant positive association was seen between CD4$^+$ T-cell count and SBP in the PWH but not in the HIV-uninfected group.

HIV status was also a significant moderator in the relationships between estimated glomerular filtration rate (eGFR) and hemoglobin with SBP (Figure S1A). A statistically significant positive association was seen between eGFR and SBP at baseline in the HIV-uninfected group but not in PWH . A similar trend was seen for albuminuria with a statistically significant positive association seen between albumin-creatinine ratio and SBP at baseline in the HIV-uninfected group but not in PWH (Figure S1B). In contrast, a stronger positive association was seen between hemoglobin and SBP in PWH than in HIV-uninfected adults (Figure S1C).

TABLE 1 Baseline characteristics for study population

	People with HIV (n = 500[a])	HIV-uninfected (n = 504[a])
	Number (%)/Median [IQR]	Number (%)/Median [IQR]
Age (y)	36 [29-43]	35 [26.5-43]
Female	343 (68.6%)	335 (66.5%)
Education		
Primary school or less	408 (81.6%)	371 (73.6%)
Secondary school (form 1-4)	75 (15.0%)	113 (22.4%)
University/college	17 (3.4%)	20 (4.0%)
Monthly income (TSh)	90 000 [33 000-181 000]	80 000 [40 000-150 000]
Mode of transport to clinic		
Private vehicle	75 (15.0%)	43 (8.5%)
Public transport	207 (41.4%)	200 (39.7%)
Walk or Bicycle	218 (43.6%)	261 (51.8%)
Manual labor	138 (27.6%)	136 (27.0%)
Last blood pressure (BP) measurement		
Within the last year	172 (34.4%)	113 (22.4%)
More than 1 y ago	45 (9.0%)	84 (16.7%)
Never	283 (56.6%)	307 (60.9%)
Antiretroviral therapy (ART) initiated immediately after enrollment		
Tenofovir, lamivudine, efavirenz	403 (80%)	N/A
Tenofovir, lamivudine, dolutegravir	31 (6.2%)	N/A
Other ART regimens	24 (4.8%)	N/A
Delayed ART initiations	42 (8.4%)	N/A
Ever used tobacco	82 (16.4%)	52 (10.3%)
Currently using tobacco	26 (5.2%)	28 (5.6%)
Ever used alcohol	352 (70.4%)	268 (53.2%)
Used alcohol in last year	182 (36.4%)	150 (29.8%)
Fruit servings/wk	2 [0.5-7]	2 [0-4]
Vegetable servings/wk	5 [2-7]	5 [2-7]
Add salt to cooking	259 (51.8%)	238 (47.2%)
Soda(s)/d	1 [1-2]	1 [1-2]
Waist circumference (cm)	78.0 [72.4-85.5]	80.5 [73.1-90.1]
Body mass index (kg/m^2)	21.6 [19.2-24.8]	22.4 [19.8-26.7]
SBP (mm Hg)	113.5 [104.0-124.5]	123 [112.0-134.0]
Low SBP at baseline (SBP < 90)	14 (2.8%)	3 (0.6%)
DBP (mm Hg)	74.5 [68.0-82.0]	78 [71.5-85.0]
Diabetes	12 (2.4%)	10 (2.0%)
Hemoglobin (g/dL)	12.2 [10.5-13.8]	13.6 [12.6-14.8]
Normal	253 (50.6%)	427 (84.7%)
Mild anemia	88 (17.6%)	30 (6.0%)
Moderate anemia	134 (26.8%)	42 (8.3%)
Severe anemia	25 (5.0%)	5 (1.0%)
eGFR < 60 mL/min/1.73 m^2	52 (10.4%)	54 (10.7%)
Albumin-creatinine ratio (mg/g)	6 [3-13.5]	4 [0-7]
Normal (<30 mg/g)	429 (85.8%)	470 (93.3%)
High (≥30 and ≤ 300 mg/g)	53 (10.6%)	28 (5.6%)
Very high (≥300 mg/g)	18 (3.6%)	6 (1.2%)
CD4$^+$ T-cell count (cells/mm^3)	412.5 [163.5-594]	883 [715.5-1068.5]
Total lymphocyte count (cells/mm^3)	1903 [1395-2404]	2123 [1763-2541]

[a]Four participants were HIV-uninfected at baseline but seroconverted during follow-up. These four participants contribute observation time to both study groups and are counted in both groups.

TABLE 2 Statistically significant associations between characteristics from Table 1 and baseline systolic blood pressure (SBP) in 1000 people with HIV and HIV-uninfected participants in Mwanza City, Tanzania

	Univariate analysis			Multivariate analysis	
	Coefficient [95% CI] SBP in mm Hg	*P*-value	Interaction[a] *P*-value	Coefficient [95% CI] SBP in mm Hg	*P*-value
HIV infection	−8.66 [−10.72,−6.59]	<.001	N/A	−6.29 [−8.29,−4.28]	N/A
Age (y)	0.54 [0.44,0.64]	<.001	.059	0.48 [0.38,0.57]	<.001
Sex (male)	5.35 [3.11,7.61]	<.001	.420	5.54 [3.23,7.85]	<.001
Fruit servings/wk	−0.49 [−0.82,−0.15]	.004	.854	−0.37 [−0.67,−0.08]	.014
Waist circumference (cm)	0.47 [0.38,0.56]	<.001	.318		
Body mass index (kg/m^2)	0.85 [0.64,1.05]	<.001	.459	0.67 [0.46,0.87]	<.001
Hemoglobin (g/dL)	2.09 [1.64,2.53]	<.001	.046	1.06 [0.57,1.54]	<.001
eGFR < 60 mL/min/1.73 m^2	6.91 [3.46,10.35]	<.001	.008		
CD4$^+$ T-cell count (cells/mm^3)	0.008 [0.005,0.011]	<.001	.005		
Manual labor	3.88 [1.50,6.26]	.001	.899		
Time of home smoke exposure (y)	0.11 [0.03,0.19]	.006	.203		

[a]Interaction effect with HIV status.

3.6 | Blood pressure changes over time

All 1000 participants were studied for blood pressure trends. Of 4155 blood pressure measurements included in this analysis, 84 were censored because participants were receiving blood pressure–lowering medications. Figure 2Adepicts the change in mean SBP from baseline over the first 2 years of study follow-up. For PWH, the average change in SBP from baseline to 24 months was 4.7 mm Hg (95% CI: 3.1-6.3 mm Hg) vs 0.4 mm Hg (−1.3 to 2.1) in controls. PWH with a CD4$^+$ T-cell count of <300 at baseline experienced a significantly greater increase in SBP from baseline than those with a higher CD4$^+$ count (Figure 2B). The trends in mean SBP and DBP from baseline to 24 months are displayed in Figures S2 and S3.

We investigated the association between all exposures in Table 1 with change in SBP from baseline to 24 months using linear regression models. Factors significantly associated with greater increases in SBP from baseline to 24 months were HIV infection, lower baseline CD4$^+$, and lower hemoglobin. In this analysis, significant effect modification was observed for baseline CD4$^+$ count ($P = .007$ for interaction), which was only significant in PWH. Neither total lymphocyte counts nor ART regimen nor delay in ART initiation were significantly associated with change in SBP from baseline to 24 months. In addition, a greater increase in CD4$^+$ count (coefficient: 0.007, $P = .023$, Figure 1B), hemoglobin (1.37, $P < .001$), waist circumference (0.52, $P < .001$), and BMI (1.71, $P < .001$) during the first 2 years of ART was significantly associated with greater increases in SBP from baseline to 24 months. In multivariate models including changes in CD4$^+$ count, hemoglobin, and waist circumference, we found clear and consistent differences in factors associated with change in SBP over 2 years according to baseline blood pressure. For PWH with SBP < 120 mm Hg at baseline, in a multivariate model including CD4$^+$ count, hemoglobin, and waist circumference, change in CD4$^+$ count remains significantly associated with change in SBP (0.007, $P = .042$) together with change in hemoglobin (1.00, $P = .003$) and waist circumference (0.34, $P = .004$). For PWH with SBP ≥120 mm Hg at baseline, in a multivariate model including the same variables, the only factor significantly associated with increase in SBP was increased waist circumference (0.83, 0.001). BMI was excluded from these models due to co-linearity with waist circumference.

From the first blood pressure measurement at enrollment through the next 2 study visits (0, 3, and 6 months), blood pressure declined in both PWH and HIV-uninfected participants. In total, 846 study participants attended all three of these visits. On the first measurement at the 1st visit, 211/846 (24.9%) had a blood pressure ≥140/90 mm Hg. In contrast, using the average of measurements at the 1st visit, only 125 (14.8%) had a blood pressure ≥140/90 mm Hg. By the 2nd and 3rd study visits, only 73 (8.6%) and 52 (6.1%) had a blood pressure that was persistently ≥140/90 mm Hg.

3.7 | Baseline SBP and mortality in PWH

Thirty-four out of 500 PWH (6.8%) died during the 2 years of follow-up. One HIV-uninfected control died. Low baseline blood pressure was significantly associated with mortality during the first 2 years of follow-up in PWH. Figure 3displays the Kaplan-Meier survival analysis of survival in PWH grouped by baseline blood pressure into three groups: SBP < 90, SBP 90-139, and SBP ≥ 140 mm Hg. Five out of 17 (29.4%) PWH with baseline blood pressure <90 mm Hg died within 2 years compared to none of the PWH with baseline blood pressure of ≥140 ($P < .0001$ by log-rank test). After adjusting for age, sex, and CD4$^+$ count, SBP at baseline < 90 mm Hg remained strongly associated with mortality

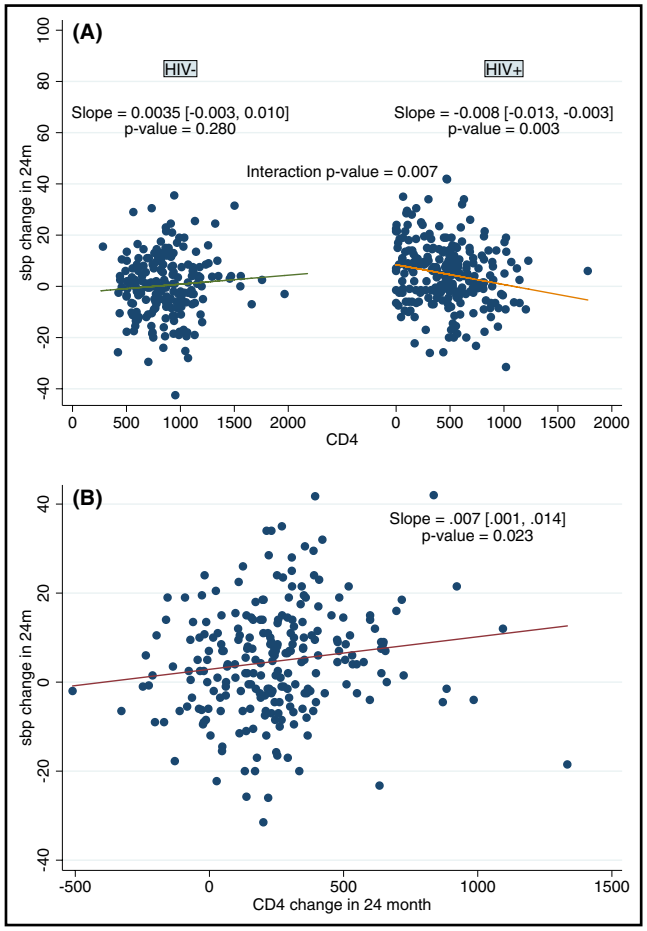

FIGURE 1 $CD4^+$ T-cell counts were significantly associated with systolic blood pressure (SBP), but only in people With HIV (PWH). Panel A. Association between baseline $CD4^+$ count and change in SBP from baseline to 24 mo in PWH (right) and HIV-uninfected adults (left). Panel B. Association between increase in $CD4^+$ T-cell count and increase in SBP during the first 2 y of ART in PWH

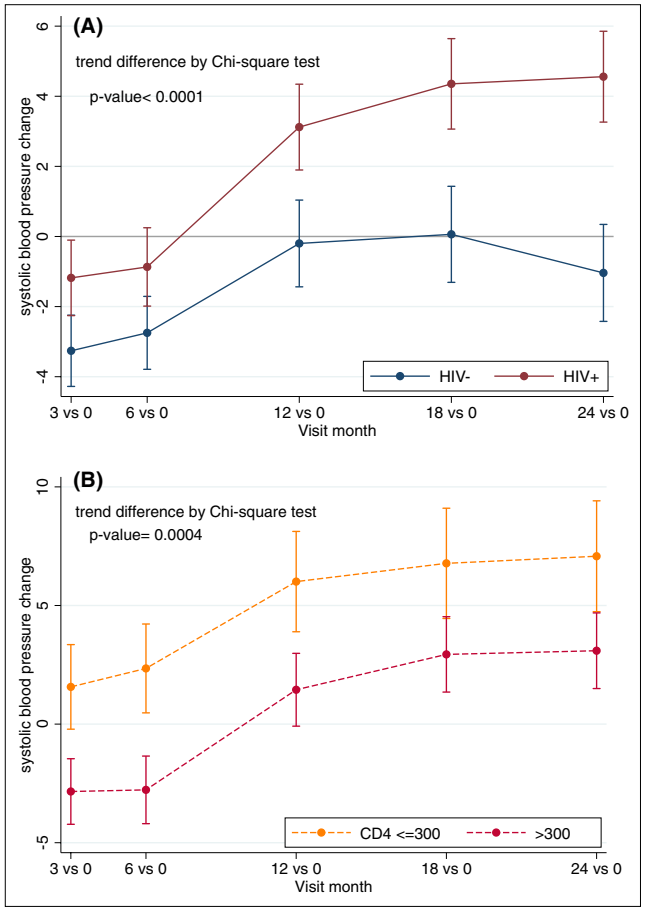

FIGURE 2 Systolic blood pressure (SBP) increased more rapidly in people with HIV (PWH) compared to controls with an even greater increase observed in PWH with low $CD4^+$ T-cell counts. Panel A. Changes in SBP from baseline during the first 2 y of antiretroviral therapy in PWH (red line) and HIV-uninfected controls (blue line). Panel B. Changes in SBP from baseline during the first 2 y of antiretroviral therapy in PWH with CD4+ ≤300 (yellow line) and CD4+ >300 (red line)

(aHR = 7.0 [2.6-19.2], *P*-value < .001). The details for these five participants are provided in Table S2. In all 5, the cause of death was tuberculosis with immune reconstitution inflammatory syndrome (IRIS) within 3 months of enrollment.

4 | DISCUSSION

In our study of 1000 young and middle-aged Tanzanian adults, PWH experienced a 4 mm Hg greater increase in SBP during the first 2 years of antiretroviral therapy (ART) than similar HIV-uninfected control participants. This result is both statistically and clinically significant. Meta-analysis in 61 prospective observational studies demonstrated that even a 2 mm Hg higher SBP in early adulthood or middle age is associated with a 10% higher lifetime risk of death from stroke and a 7% higher risk of death from ischemic heart disease.[18] Meta-analysis of more clinical trials of antihypertensive treatment in this age-group has confirmed that a 5 mm Hg reduction in SBP prevents cardiovascular events and reduces all-cause mortality.[19] These results suggest that the early ART period may represent a critical window of opportunity for interventions to reduce long-term cardiovascular risk in PWH.

Before ART initiation, PWH had a significantly lower blood pressure than HIV-uninfected adults. This combination of lower blood pressure before ART initiation and a more rapid increase in blood pressure after ART initiation leads us to an important question—why are the dynamics of blood pressure different in PWH in the early ART period? The answer to this question likely involves a complex interplay between traditional and HIV-specific risk factors such as immune reconstitution.[20] Several recent cross-sectional studies have shown that PWH on established ART have the same or less hypertension than HIV-uninfected controls.[21-23] Other studies, however, have shown higher rates of hypertension in PWH.[24] Our results indicate that further research should focus on the early ART period.

Among PWH, lower baseline $CD4^+$ T-cell counts were significantly associated with lower baseline blood pressure, and greater increases in $CD4^+$ T-cell counts during the first 2 years of ART were

associated with greater increases in blood pressure in participants with SBP < 120 mm Hg at baseline, even after adjusting for potential confounders. Total lymphocyte counts, on the other hand, were not associated with blood pressure. Of note, a return to good health marked by rising hemoglobin and weight appears to explain some, but not all of the association that we observed between changes in $CD4^+$ T-cell count and increases in blood pressure. These results imply that increases in blood pressure in the early ART period might be driven by rapid changes in T-cell immunity during this period (Figure 4). Mice lacking T cells exhibit reduced blood pressure increases in response to salt and angiotensin II infusion.[25] In humanized mice given activated human T cells, by contrast, the $CD4^+$ T cells invade aorta and kidney and produce cytokines IL-17A and IFN-gamma, which contribute to hypertension.[26] Similarly in mice with hypertension, $CD4^+$ T cells produce IL-17A in the kidney and aorta and blocking IL-17A reduces the blood pressure.[27] Therefore, ART-naïve PWH may have lower blood pressure due to depletion of $CD4^+$ T cells. After ART initiation and immune reconstitution, abnormally activated $CD4^+$ T cells may invade the aorta and the kidney, leading to a rapid rise in blood pressure. Alternatively, rapid changes in $CD4^+$ T-cell immunity could induce changes in $CD8^+$ T cells or monocytes that are also known to be involved in the pathophysiology of hypertension.

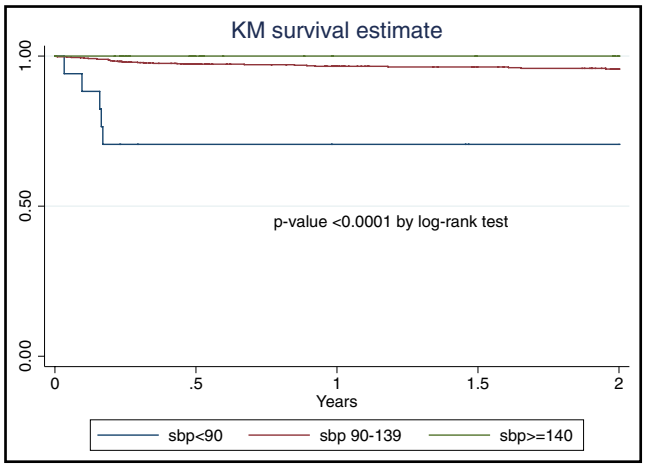

FIGURE 3 Kaplan-Meier curve for survival of people with HIV during the first 2 y of follow-up according to the baseline systolic blood pressure (SBP)

Several determinants of blood pressure differed significantly by HIV status including hemoglobin, reduced eGFR, and albuminuria. Hemoglobin, for example, was strongly associated with SBP. The regression coefficient for the relationship between hemoglobin and SBP and PWH was twice as great in PWH compared to HIV-uninfected adults. Among PWH in our study, >30% had moderate or severe anemia, and a reduction of hemoglobin of 5 g/dL was associated with a 10 mm Hg lower SBP. Studies from the general population have reported a small but statistically significant association between hemoglobin and blood pressure.[28,29] Higher hemoglobin may directly promote arterial stiffness or may reduce vascular nitric oxide levels leading to vasoconstriction,[30,31] and HIV may promote similar changes.[32] This finding deserves further investigation.

We found that both SBP and DBP dropped dramatically between the first, second, and third visits at the HIV clinic (Tables S2 and S3). Furthermore, only 25% of participants whose first blood pressure measurement was elevated had persistent hypertension on three consecutive visits. This could be due to anxiety in a population where blood pressure measurement is rarely performed (nearly 60% of our participants had never had their blood pressure measured).[33] Accurate measurement of blood pressure is a cornerstone of hypertension management. Therefore, as HIV programs in Africa begin to integrate hypertension care into clinical practice, these programs must ensure that standard procedures for measuring multiple blood pressures on different days will be followed.

PWH with SBP < 90 mm Hg at the time of ART initiation should receive special medical attention. Our findings confirm a recent publication from a cohort study of 816 PWH in Haiti in which SBP < 90 mm Hg before ART initiation was associated with a twofold increased odds of mortality.[7] Low blood pressure before ART initiation may be secondary to an undiagnosed infection, which could progress to septic shock and/or severe IRIS after ART initiation.[34] PWH with SBP < 90 mm Hg in before ART initiation should undergo a thorough diagnostic workup for occult infections with close follow-up. Corticosteroid treatment should be considered in those with tuberculosis to prevent death due to immune reconstitution inflammatory syndrome (IRIS).[35]

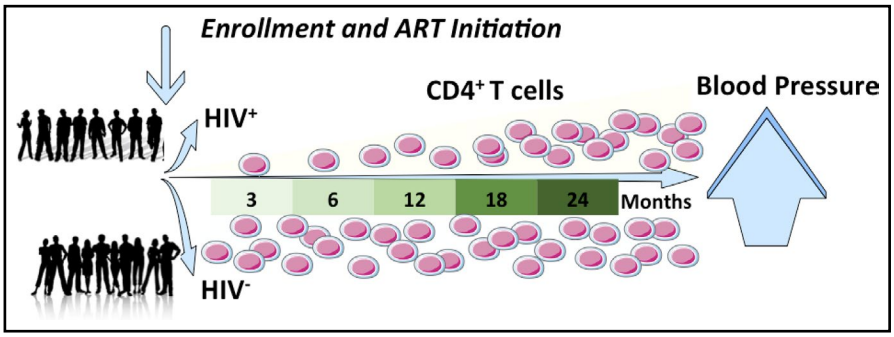

FIGURE 4 Graphical abstract. In people with HIV who were enrolled before initiation of antiretroviral therapy (ART) and followed for 24 mo, blood pressure increased significantly more than in HIV-uninfected control participants of similar age and gender. This increase in blood pressure was significantly associated with increases in $CD4^+$ T cells, both on average and within individuals

Our study has limitations. HIV viral loads are not measured at the time of ART initiation in Tanzania and, therefore, were not available as part of the baseline data. Of note, HIV viral load has not been strongly associated with blood pressure in prior studies.[3,4] In addition, although we did not observe a significant association between ART exposure and blood pressure, a longer duration of follow-up may be needed to observe such effects. The results of our study are likely generalizable to other populations of PWH in sub-Saharan Africa but may not be generalizable to PWH living in high-income countries where early diagnosis and treatment of HIV are more common and severe immunosuppression is rare.

5 | CONCLUSIONS

Our analysis of blood pressure in the pre-ART and early ART period in PWH and HIV-uninfected adults has revealed several exciting new findings. First, immune-suppressed PWH had a significantly lower blood pressure before ART initiation but a significantly greater increase in blood pressure during the first 2 years of ART. Second, lower blood pressure before ART initiation and greater increases in blood pressure were strongly associated with $CD4^+$ T-cell counts. Third, PWH with an SBP of <90 mm Hg at the time of ART initiation had a 30% risk of death in the first 3 months of ART. Further research is needed to determine the mechanisms underlying the association of blood pressure and T cells in the early ART period. In addition, blood pressure measurement must be regularly and carefully measured in HIV clinics and PWH with low SBP should receive careful investigation and close monitoring.

ACKNOWLEDGMENTS

We would like to acknowledge all of our participants, without whom this work would be impossible, as well as our colleagues at Bugando Medical Center who have lent their support to this research.

CONFLICT OF INTEREST

No conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

KR contributed to study design, data collection, data analysis, data interpretation, and manuscript preparation, and revised the manuscript for important intellectual content. BD contributed to study conception and study design, and revised the manuscript for important intellectual content. JK contributed to study conception, study design, data collection, and manuscript preparation, and revised the manuscript for important intellectual content. AK contributed to data analysis, data interpretation, and manuscript preparation, and revised the manuscript for important intellectual content. AM contributed to study conception and study design, and revised the manuscript for important intellectual content. CM contributed to data analysis, data interpretation, and manuscript preparation, and revised manuscript for important intellectual content. ML contributed to study design, data analysis, data interpretation, and manuscript preparation, and revised the manuscript for important intellectual content. SK contributed to study conception, study design, data interpretation, and manuscript preparation, and revised the manuscript for important intellectual content. RP contributed to study conception, study design, data collection, data analysis, data interpretation, and manuscript preparation, and revised the manuscript for important intellectual content. All authors approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Reis KG, Desderius B, Kingery J, et al. Blood pressure, T cells, and mortality in people with HIV in Tanzania during the first 2 years of antiretroviral therapy. *J Clin Hypertens*. 2020;22:1554–1562. https://doi.org/10.1111/jch.13975