

# Higher Prevalence of Hypertension in HIV-1-Infected Patients on Combination Antiretroviral Therapy Is Associated With Changes in Body Composition and Prior Stavudine Exposure

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(See the HIV/AIDS Major Article by Okeke et al on pages 242–8.)

**Background.** Individuals infected with human immunodeficiency virus (HIV) have a higher risk of cardiovascular disease, potentially partly mediated by a higher prevalence of hypertension. We therefore examined the prevalence and determinants of hypertension in HIV-1-infected patients compared with appropriate HIV-negative controls.

**Methods.** Data from 527 HIV-1-infected and 517 HIV-uninfected participants at the time of enrollment into the ongoing AGE<sub>h</sub>IV Cohort Study were analyzed. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg, and/or self-reported use of antihypertensive drugs.

**Results.** Hypertension prevalence was higher among HIV-1-infected individuals compared with controls (48.2% vs 36.4%; odds ratio [OR], 1.63; 95% confidence interval [CI], 1.27–2.09). In logistic regression models adjusted for age, sex, ethnicity, family history of hypertension, smoking, alcohol use, physical activity, and body mass index, the association between HIV and hypertension remained statistically significant (OR<sub>HIV</sub>, 1.65; 95% CI, 1.25–2.19), but was attenuated after additional adjustment for waist-to-hip ratio (OR<sub>HIV</sub>, 1.29; 95% CI, .95–1.76). Among HIV-1-infected individuals, particularly among those with mono/dual nucleoside reverse transcriptase inhibitor therapy prior to combination antiretroviral therapy, stavudine exposure was independently associated with hypertension (OR<sub>stavudine</sub>, 1.54; 95% CI, 1.04–2.30). This association was attenuated after additional adjustment for either waist-to-hip ratio (OR<sub>stavudine</sub>, 1.30; 95% CI, .85–1.96) or hip circumference (OR<sub>stavudine</sub>, 1.40; 95% CI, .93–2.11).

**Conclusions.** Our findings suggest that changes in body composition, involving both abdominal obesity and stavudine-induced peripheral lipoatrophy, might contribute to the higher prevalence of hypertension in HIV-1-infected patients.

**Clinical Trials Registration.** NCT01466582.

**Keywords.** HIV-1 infection; hypertension; obesity; lipodystrophy; stavudine.

Hypertension is an important contributor to cardiovascular disease (CVD) among individuals infected with human immunodeficiency virus (HIV) [1]. Previously reported hypertension prevalence varies from 13% to 49% in HIV-infected populations, but studies comparing the prevalence of hypertension

among HIV-infected individuals and controls show conflicting results [2–7]. Common risk factors such as age, sex, and body mass index (BMI) [4–9], immune activation and inflammation [10], and antiretroviral drug use and immunodeficiency could contribute to the higher prevalence of hypertension in HIV-infected individuals [5, 7, 11–13].

To further elucidate these issues, we performed a cross-sectional analysis of HIV-1-infected and HIV-uninfected individuals participating in the AGE<sub>h</sub>IV Cohort Study, which aimed (1) to determine the prevalence of hypertension in a middle-aged HIV-1-infected population, predominantly receiving combination antiretroviral therapy (cART); (2) to assess whether HIV-1-positive serostatus is independently associated with hypertension; and, if so, (3) to identify HIV-related determinants that might explain a higher prevalence of hypertension among HIV-1-infected individuals.

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<sup>a</sup>The members of the AGE<sub>h</sub>IV Cohort Study Group are listed in the Supplementary Appendix.

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## METHODS

### Study Participants and Design

The AGE<sub>h</sub>IV Cohort Study is an ongoing prospective comparative cohort study investigating age-related comorbidities and their risk factors in HIV-1-infected patients and HIV-uninfected controls. HIV-1-infected individuals were recruited from the HIV outpatient clinic of the Academic Medical Center in Amsterdam, the Netherlands. An HIV-uninfected control group with similar demographic and behavioral characteristics was recruited from the Amsterdam Cohort Studies on HIV/AIDS and among individuals attending the sexual health clinic at the Amsterdam Public Health Service. Inclusion criteria were age  $\geq 45$  years and laboratory-confirmed (HIV-1-infected participants) or laboratory-rejected (HIV-uninfected controls) HIV-1 infection, resulting in 598 HIV-1-infected and 550 HIV-uninfected participants. Participants attend biennial study visits; baseline study visits took place between 2010 and 2012. All participants provided written informed consent and the study was approved by the local ethics review board (ClinicalTrials.gov identifier NCT01466582).

### Measures

Participants underwent standardized screening for age-related comorbidities, organ dysfunction, and risk factors, details of which have been previously reported [14]. Standardized screening included blood pressure measurements, anthropometric measurements, and collection of blood and urine samples for extensive laboratory testing, including serum lipids, glycated hemoglobin (HbA1c), glucose, markers of systemic inflammation (high-sensitivity C-reactive protein [hs-CRP]), monocyte activation (soluble CD163 [sCD163], soluble CD14 [sCD14]), CD4 cell count, plasma HIV-1 RNA levels, and hepatitis B virus and hepatitis C virus serostatus. Participants were requested to complete a questionnaire covering demographic characteristics, medication use, medical (family) history, physical activity, and alcohol/substance use. Detailed (historical) information regarding HIV infection and antiretroviral therapy (ART) was obtained from the database of the Dutch HIV Monitoring Foundation [15].

Seated resting brachial blood pressure was measured 3 times at 1-minute intervals after a 5-minute rest using an automated device (Omron 705-IT, Hoofddorp, the Netherlands). Mean systolic and diastolic blood pressure (SBP and DBP, respectively) were defined as the mean of the second and third measurement. Hypertension was defined as SBP  $\geq 140$  mmHg, DBP  $\geq 90$  mmHg, and/or self-reported use of antihypertensive medication. Normotensive individuals who received antihypertensive drugs for a different indication, including renal disease ( $n = 5$ ) or liver cirrhosis ( $n = 1$ ), were classified as normotensive. Severity of hypertension was graded according to American Society of Hypertension guidelines [16]. Hypertension control was defined as SBP  $< 140$  mmHg and DBP  $< 90$  mmHg among individuals using antihypertensive medication.

Waist and hip circumference were measured in duplicate according to the World Health Organization protocol, and means were calculated [17]. Diabetes was considered present if the HbA1c level was  $\geq 48$  mmol/mol, if blood glucose was elevated (nonfasting  $\geq 11.1$  mmol/L, fasting  $\geq 7.0$  mmol/L), and/or if an individual was using antidiabetic medication [18]. Physical activity was defined according to Dutch healthy physical activity guidelines (ie, "Combinorm"): performing moderate physical activity  $\geq 5$  days per week for  $\geq 30$  minutes, and/or heavy physical activity  $\geq 3$  days per week for  $\geq 20$  minutes [19]. Heavy alcohol use was defined as alcohol intake  $\geq 5$  units/day for men or  $\geq 3$  units/day for women. CVD was considered present in participants with a self-reported and validated diagnosis of angina pectoris, myocardial infarction, ischemic cerebrovascular disease, and peripheral arterial disease as previously described [14].

### Statistical Analysis

Stata software (version 12.1; StataCorp, College Station, Texas) was used for statistical analyses. Group comparisons were performed using  $\chi^2$ , Fisher's exact, Wilcoxon rank-sum, or non-parametric trend tests, as appropriate.

Multivariable logistic regression was performed using a stepwise model selection approach to assess whether HIV-1-positive serostatus was independently associated with hypertension and to identify potential traditional and HIV-related determinants of hypertension. Models were adjusted for potential confounders in 2 steps: demographic confounders only (age, sex, and ethnicity) (model 1); and all common predictors of hypertension (age, sex, ethnicity, positive family history for hypertension, smoking status, physical activity, heavy alcohol use, and BMI) (model 2). Subsequently, biologically plausible mediators of the association between HIV and hypertension were explored in multivariable model 2, including diabetes mellitus, waist-to-hip ratio, markers of systemic inflammation, and HIV/ART-related variables. Missing data of independent covariates were handled by multiple imputation. Effect modification was evaluated for each of the risk factors with regard to HIV infection, and collinearity of independent variables was tested. Odds ratios (ORs), corresponding 95% confidence intervals (95% CIs), and 2-sided *P* values are reported.

A sensitivity analysis was conducted by excluding participants with mono/dual nucleoside reverse transcriptase inhibitor (NRTI) exposure prior to cART initiation.

## RESULTS

### Cohort Characteristics

A total of 598 HIV-1-infected and 550 HIV-uninfected participants were enrolled in the AGE<sub>h</sub>IV Cohort Study. We excluded 104 patients with missing data regarding medication use due to incomplete or unavailable questionnaires, or blood pressure measurements (71 HIV-1-infected, 33 HIV-uninfected). Excluded individuals were more likely to be female (24.0% vs 12.9%) and of African descent (28.7% vs 8.9%); excluded

**Table 1. Characteristics of Participants at Time of Enrollment Into the AGE<sub>IV</sub> Cohort Study**

Characteristic	HIV-1-Infected Individuals (n = 527)	HIV-Uninfected Individuals (n = 517)	P Value
<b>Demographics</b>			
Age, y	52.9 (48.3–59.6)	52.2 (47.9–58.1)	.186 <sup>a</sup>
Male sex	467 (88.6)	442 (85.5)	.133 <sup>b</sup>
African descent <sup>c</sup>	64 (12.1)	29 (5.6)	<.001 <sup>b</sup>
MSM	393 (74.6)	362 (70.0)	.100 <sup>b</sup>
<b>Traditional CVD risk factors</b>			
Smoking status			.022 <sup>d</sup>
Ever smoker	184 (34.9)	201 (38.9)	
Current smoker	169 (32.1)	126 (24.4)	
Heavy alcohol use <sup>e</sup>	26 (5.0)	37 (7.2)	.138 <sup>b</sup>
Family history of hypertension	256 (49.6)	225 (43.7)	.057 <sup>b</sup>
Physically active <sup>f</sup>	230 (44.2)	272 (52.8)	.005 <sup>b</sup>
BMI, kg/m <sup>2</sup>	24.2 (22.3–26.6)	24.5 (22.9–27.0)	.017 <sup>a</sup>
Underweight (<20)	43 (8.2)	17 (3.3)	.137 <sup>d</sup>
Normal weight (20 to <25)	267 (50.8)	281 (54.4)	
Overweight (25 to <30)	175 (33.3)	168 (32.5)	
Obese (≥30)	41 (7.8)	51 (9.9)	
Waist-to-hip ratio	0.97 (0.92–1.02)	0.92 (0.87–0.96)	<.001 <sup>a</sup>
Abnormal waist-to-hip ratio (men, ≥0.9; women, ≥0.85)	440 (83.8)	322 (62.7)	<.001 <sup>b</sup>
Waist circumference, cm	93.6 (86.3–100.6)	90.8 (84.8–97.6)	.002 <sup>a</sup>
Hip circumference, cm	96.3 (92.0–101.0)	99.0 (95.6–103.2)	<.001 <sup>a</sup>
Prevalence of diabetes mellitus	32 (6.1)	20 (3.9)	.108 <sup>b</sup>
eGFR category <sup>h</sup> , mL/min/1.73 m <sup>2</sup>			.965 <sup>d</sup>
Normal (≥90)	295 (57.0)	284 (55.7)	
Mildly decreased (60 to <90)	199 (38.4)	215 (42.2)	
Mildly to moderately decreased (45 to <60)	18 (3.5)	8 (1.6)	
Moderately to severely decreased (30 to <45)	4 (0.8)	3 (0.6)	
Severely decreased (15 to <30)	2 (0.4)	0 (0)	
Kidney failure (<15)	0 (0)	0 (0)	
Prevalence of CVD	53 (10.1)	27 (5.2)	.003 <sup>b</sup>
<b>Inflammation/immune activation markers and hepatitis (co)infection</b>			
hs-CRP, mg/L	1.5 (0.7–3.5)	1.0 (0.6–1.9)	<.001 <sup>a</sup>
sCD14, ng/mL	1576 (1310–2012)	1355 (1077–1738)	<.001 <sup>a</sup>
sCD163, ng/mL	289 (207–420)	253 (183–343)	<.001 <sup>a</sup>
<b>Hepatitis (co)infection</b>			
Hepatitis B (HBsAg positive)	20 (3.8)	3 (0.6)	<.001 <sup>g</sup>
Hepatitis C (HCV RNA positive)	13 (2.5)	4 (0.8)	.048 <sup>g</sup>
<b>HIV-related parameters</b>			
Years since known HIV-1 infection	12.2 (6.6–17.2)	...	
<b>ART exposure/regimen</b>			
On cART at enrollment	499 (94.7)	...	
Mono/dual NRTI therapy prior to cART initiation	106 (20.1)	...	
Prior stavudine exposure	196 (37.2)	...	
Years of stavudine exposure among those with mono/dual NRTI therapy prior to cART initiation <sup>i</sup>	4.4 (2.1–6.7)	...	
Years of stavudine exposure among those without mono/dual NRTI therapy prior to cART initiation <sup>i</sup>	3.3 (1.4–4.7)	...	
Prior zidovudine exposure	313 (59.4)	...	
Plasma HIV-RNA <200 copies/mL within 4 mo before or at enrollment <sup>l</sup>	493 (99.6)	...	
Prior AIDS	162 (30.7)	...	

Table 1 continued.

Characteristic	HIV-1-Infected Individuals (n = 527)	HIV-Uninfected Individuals (n = 517)	P Value
CD4 count, cells/ $\mu$ L			
Mean CD4 count in year prior to enrollment	570 (435–745)	. . .	
Nadir CD4 count	180 (80–260)	. . .	

Data are presented as No. (%) or median (interquartile range).

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; cART, combination antiretroviral therapy; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; MSM, men who have sex with men; NRTI, nucleoside reverse transcriptase inhibitor; sCD14, soluble CD14; sCD163, soluble CD163.

<sup>a</sup> Wilcoxon rank-sum test.

<sup>b</sup>  $\chi^2$  test.

<sup>c</sup> Participants were classified as "African descent" if the birth country of an individual and  $\geq 1$  parent is Suriname, Netherlands Antilles, or sub-Saharan Africa; or if the birth country of an individual or both parents is Suriname, Netherlands Antilles, or sub-Saharan Africa and an Advanced Glycation Endproducts-reader-reader measurement is not available due to low reflection as a result of a dark skin.

<sup>d</sup> Nonparametric trend test.

<sup>e</sup> Heavy alcohol use was defined as (nearly) daily alcohol intake  $\geq 5$  units for men or  $\geq 3$  units for women.

<sup>f</sup> Physically active was defined as  $\geq 5$  days per week moderate physical activity ( $\geq 30$  minutes) and/or  $\geq 3$  days per week heavy physical activity ( $\geq 20$  minutes).

<sup>g</sup> Fisher exact test.

<sup>h</sup> The eGFR was classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation was used to estimate the glomerular filtration rate.

<sup>i</sup> Exclusively individuals ever exposed to stavudine were included to describe cumulative exposure to stavudine among ART-experienced (n = 91) and ART-naive (n = 104) prior to cART initiation.

<sup>j</sup> Exclusively HIV-1-infected individuals who were using cART at enrollment were included to describe the number of patients with a viral load  $< 200$  copies/mL.

HIV-1-infected individuals had a slightly lower median nadir CD4 cell count (130 vs 180 cells/ $\mu$ L).

Cohort characteristics of 527 HIV-1-infected and 517 HIV-uninfected participants included in the current analysis are shown in Table 1. Both groups were of comparable age (median, 52.7 years) and sex (87.1% male). HIV-1-infected individuals were more often of African descent, were more likely to smoke, were less often physically active, and had a higher prevalence of CVD. Despite their slightly lower median BMI, HIV-1-infected individuals had a higher median waist-to-hip ratio than uninfected controls, especially those exposed to stavudine (Figure 1A). HIV-1-infected individuals had a larger waist circumference (Figure 1B), independent of their cART history, and those with prior stavudine exposure demonstrated a smaller hip circumference than HIV-uninfected individuals or HIV-1-infected individuals without prior exposure to stavudine (Figure 1C).

Nearly all HIV-1-infected participants were on cART, had an undetectable plasma HIV-1 RNA load, and had experienced substantial immune recovery on cART (median nadir CD4 count, 180 cells/ $\mu$ L; median CD4 count at enrollment, 570 cells/ $\mu$ L); 20.1% had been exposed to mono/dual NRTI therapy prior to cART initiation (nearly all of whom were exposed to stavudine), and 37.2% had previously used stavudine. Median exposure to stavudine was longer among those with mono/dual NRTI therapy prior to cART initiation (4.4 years vs 3.3 years;  $P = .001$ ; Table 1).

### Prevalence of Hypertension

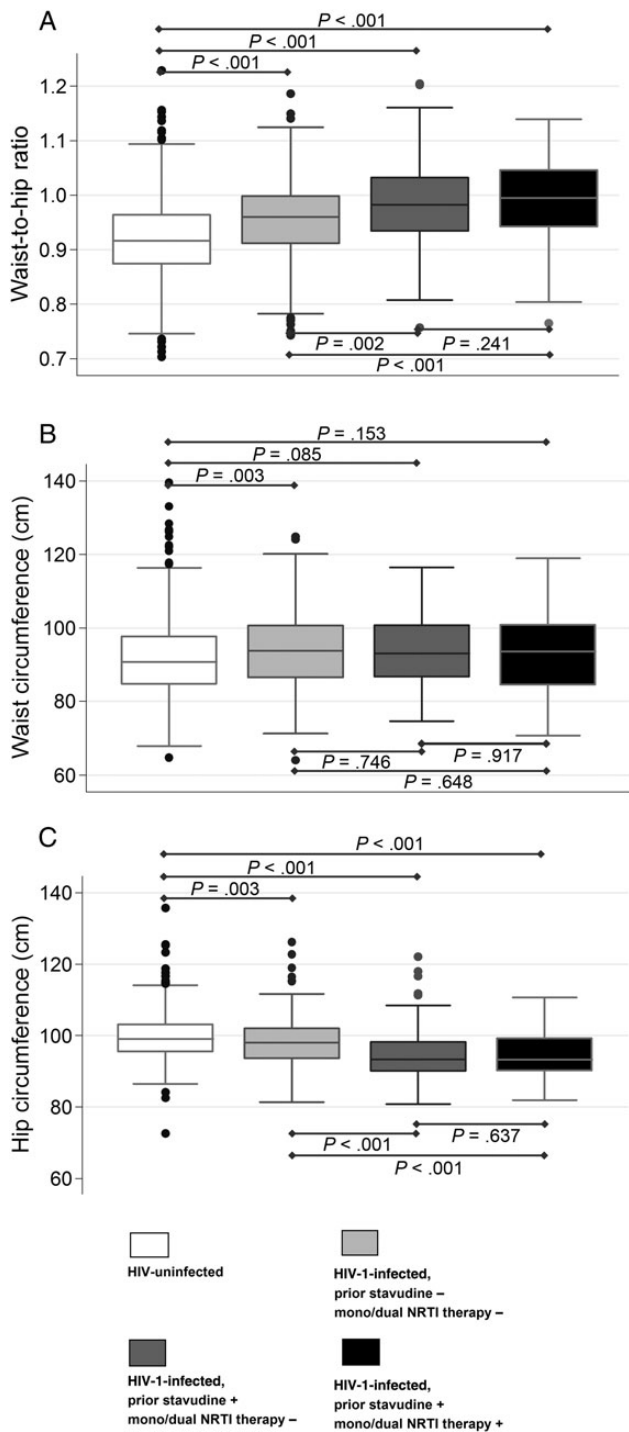
Hypertension was present among 254 HIV-1-infected (48.2%) and 188 HIV-uninfected individuals (36.4%; OR<sub>HIV</sub>, 1.63; 95% CI, 1.27–2.09;  $P < .001$ ). The prevalence of hypertension was higher in HIV-1-infected individuals across the entire age

range (Figure 2). HIV-1-infected patients received significantly more antihypertensive treatment (22.8%) compared with HIV-uninfected individuals (13.9%;  $P < .001$ ) and had a comparable rate of hypertension control. SBP did not differ between groups, whereas DBP was higher in HIV-1-infected patients (Table 2).

### Determinants of Hypertension

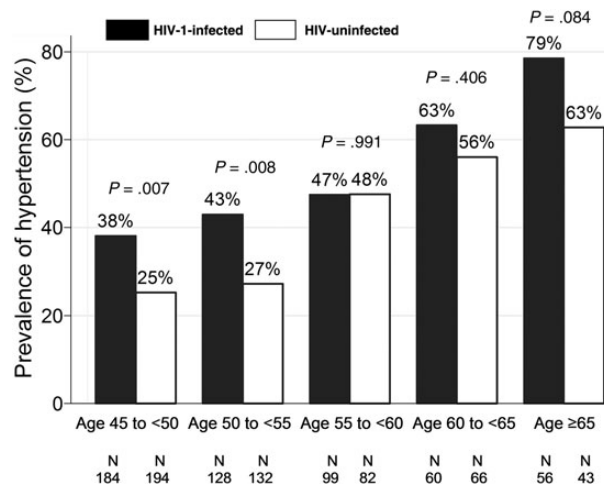
HIV-1-positive serostatus remained significantly associated with an increased prevalence of hypertension after adjustment for age, sex, and ethnicity (OR<sub>HIV</sub>, 1.52; 95% CI, 1.17–1.98;  $P = .002$ ; Table 3, model 1), as well as after adjustment for all common predictors of hypertension (OR<sub>HIV</sub>, 1.65; 95% CI, 1.25–2.19;  $P < .001$ ; Table 3, model 2). After additional adjustment for waist-to-hip ratio, the association between HIV and hypertension was attenuated and no longer statistically significant (OR<sub>HIV</sub>, 1.29; 95% CI, .95–1.76;  $P = .098$ ; Table 3, model 3). Both waist circumference and hip circumference were associated with hypertension, but waist-to-hip ratio fitted best to our data (Table 3, models 4 and 5, respectively).

No statistically significant interactions were found between HIV and any of the variables found to be associated with hypertension in the fully adjusted model. Analysis of the separate components of waist-to-hip ratio revealed a borderline statistically significant interaction between HIV-1-positive serostatus and hip circumference ( $P_{\text{interaction}} = .081$ ), but not waist circumference. When analyzing the HIV-1-infected cohort separately, hip circumference was significantly negatively associated with hypertension (OR, 0.93 per 1 cm greater hip circumference; 95% CI, .88–.98;  $P = .004$ ), which was not the case in HIV-uninfected individuals (OR, 0.99 per 1 cm; 95% CI, .94–1.05;  $P = .752$ ). To further explore this borderline significant interaction, we assessed



**Figure 1.** Distribution of waist-to-hip ratio (A), waist circumference (B), and hip circumference (C) among different subgroups of participants of the AGE<sub>IV</sub> Cohort Study, classified according to human immunodeficiency virus (HIV) serostatus, prior stavudine exposure, and mono/dual nucleoside reverse transcriptase inhibitor (NRTI) therapy prior to combination antiretroviral therapy initiation (Wilcoxon rank-sum test *P* values).

the effect of prior thymidine analogue exposure in the HIV-1-infected group, and found that the negative association between hip circumference and hypertension was significant among those with prior exposure to stavudine (OR, 0.89 per 1 cm; 95% CI,



**Figure 2.** Prevalence of hypertension per age group among human immunodeficiency virus (HIV)-1-infected and HIV-uninfected participants of the AGE<sub>IV</sub> Cohort Study ( $\chi^2$  test *P* values).

.84–.95; *P* < .001), but not in those without stavudine exposure (OR, 0.97 per 1 cm; 95% CI, .92–1.03; *P* = .321). The interaction between hip circumference and prior stavudine exposure was statistically significant (*P*<sub>interaction</sub> = .003). Among HIV-1-infected individuals, prior stavudine exposure was significantly associated with hypertension in the model while adjusting for all established risk factors (OR<sub>stavudine</sub>, 1.54; 95% CI, 1.04–2.30; *P* = .033; Table 3, model 2). This association was attenuated after further adjustment for waist-to-hip ratio (OR<sub>stavudine</sub>, 1.30; 95% CI, .85–1.96; *P* = .224; Table 3, model 3) or hip circumference (OR<sub>stavudine</sub>, 1.40; 95% CI, .93–2.11; *P* = .109; Table 3, model 5), but not after adjustment for waist circumference (Table 3, model 4). No interaction was found between hip circumference and prior zidovudine exposure.

Subsequently, multivariable models with adjustment for established risk factors were used to explore various HIV-related determinants of hypertension, but years since diagnosis of HIV-1 infection, years since ART initiation, cumulative exposure to protease inhibitors, prior exposure to zidovudine, clinical AIDS, current or nadir CD4 count, cumulative duration of immunodeficiency (defined as CD4 count <200 cells/ $\mu$ L, or alternative cutoffs, ie, less than 50, 100, 350, or 500 cells/ $\mu$ L), and HIV-1 RNA <200 copies/mL were not independently associated with hypertension (data not shown).

Exploration of other potential determinants of hypertension—that is, markers of systemic inflammation (hs-CRP), monocyte activation (sCD163 and sCD14), chronic viral hepatitis, diabetes mellitus, and substance abuse—also did not reveal any statistically significant associations (data not shown).

#### Sensitivity Analysis

In a sensitivity analysis, excluding HIV-1-infected individuals who were exposed to mono/dual NRTI therapy prior to cART

**Table 2. Hypertension and Blood Pressure Measurements Among Human Immunodeficiency Virus (HIV)-1-Infected and HIV-Uninfected Participants in the AGE<sub>IV</sub> Cohort Study**

Hypertension and blood pressure measurements	HIV-1-Infected Individuals (n = 527)	HIV-Uninfected Individuals (n = 517)	P Value
Hypertension prevalence	254 (48.2)	188 (36.4)	<.001 <sup>a</sup>
Antihypertensive treatment	120 (22.8)	72 (13.9)	<.001 <sup>a</sup>
≥3 antihypertensives	23 (4.4)	14 (2.7)	.148 <sup>a</sup>
Hypertension control <sup>b</sup>	56 (47.1)	30 (41.7)	.468 <sup>a</sup>
Blood pressure measurement, mmHg <sup>c</sup> , median (IQR)			
SBP	132 (122–143)	130 (122–139)	.135 <sup>d</sup>
DBP	81 (74–87)	78 (72–84)	<.001 <sup>d</sup>
MAP	97 (90–106)	95 (89–102)	.003 <sup>d</sup>
Classification of blood pressure measurements <sup>c,e</sup>			
Normotension	78 (19.2)	83 (18.7)	
Prehypertension	195 (47.9)	246 (55.3)	
Stage 1 hypertension	103 (25.3)	91 (20.5)	
Stage 2 hypertension	31 (7.6)	25 (5.6)	

Data are presented as No. (%) unless otherwise specified.

Abbreviations: DBP, diastolic blood pressure; HIV, human immunodeficiency virus; IQR, interquartile range; MAP, mean arterial pressure; SBP, systolic blood pressure.

<sup>a</sup>  $\chi^2$  test.

<sup>b</sup> Hypertension control was defined as a blood pressure <140/90 mmHg among individuals using antihypertensive medication.

<sup>c</sup> Mean blood pressure of last 2 measurements was used, and participants using antihypertensive drugs were excluded.

<sup>d</sup> Wilcoxon rank-sum test.

<sup>e</sup> Blood pressure classification according to American Society of Hypertension guidelines (SBP/DBP): normotension, <120/80 mmHg; prehypertension, 120/80 mmHg–140/90 mmHg; stage 1 hypertension, 140/90 mmHg–160/100 mmHg; stage 2 hypertension, ≥160/100 mmHg.

<sup>f</sup> Nonparametric trend test.

initiation, HIV-1-positive serostatus remained associated with an increased prevalence of hypertension after adjustment for potential confounders (OR, 1.44; 95% CI, 1.07–1.94;  $P = .015$ ; model 2). Again, after additional adjustment for waist-to-hip ratio, the association between HIV and hypertension was attenuated and no longer statistically significant (OR, 1.20; 95% CI, .87–1.65;  $P = .256$ ; model 3). However, in contrast to the analysis of the complete study population, no interaction was found between HIV serostatus and hip circumference. Furthermore, the association of hypertension with prior exposure to stavudine was no longer statistically significant among HIV-1-infected individuals without prior mono/dual NRTI therapy (OR, 1.05; 95% CI, .64–1.72;  $P = .840$ ).

## DISCUSSION

HIV-1-infected individuals had a higher prevalence of hypertension than HIV-uninfected controls with comparable risk behavior and demographic characteristics. HIV-1-positive serostatus was independently associated with hypertension, even after adjustment for known predictors. Additional adjustment for waist-to-hip ratio attenuated the association with HIV, suggesting that a change in body composition in HIV-1-infected individuals may be an important contributor to the association between HIV and

**Table 3. Logistic Regression Models Assessing the Association Between Human Immunodeficiency Virus (HIV)-1-Positive Serostatus and Hypertension and HIV-Specific Variables**

Model	OR (95% CI)	P Value
All individuals		
HIV-1-positive serostatus		
Model 1 <sup>a</sup>	1.52 (1.17–1.98)	.002
Model 2 <sup>b</sup>	1.65 (1.25–2.19)	<.001
Model 3 <sup>c</sup>	1.29 (.95–1.76)	.098
Model 4 <sup>d</sup>	1.48 (1.10–1.97)	.009
Model 5 <sup>e</sup>	1.57 (1.18–2.10)	.002
HIV-1-infected individuals only		
Prior stavudine exposure		
Model 2 <sup>b</sup>	1.54 (1.04–2.30)	.033
Model 3 <sup>c</sup>	1.30 (.85–1.96)	.224
Model 4 <sup>d</sup>	1.50 (1.01–2.24)	.047
Model 5 <sup>e</sup>	1.40 (.93–2.11)	.109

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

<sup>a</sup> Model 1 is adjusted for age, sex, and ethnicity.

<sup>b</sup> Model 2 is adjusted for age, sex, ethnicity, family history of hypertension, smoking status, heavy alcohol use, physical activity, and body mass index.

<sup>c</sup> Model 3 is adjusted for all variables in model 2, plus waist-to-hip ratio.

<sup>d</sup> Model 4 is adjusted for all variables in model 2, plus waist circumference.

<sup>e</sup> Model 5 is adjusted for all variables in model 2, plus hip circumference.

hypertension. Interestingly, both waist and hip circumference, which may be expressions of abdominal obesity and atrophy of subcutaneous fat, were associated with HIV-related hypertension. The negative association between hip circumference and hypertension among HIV-1-infected individuals appears to be driven by prior exposure to stavudine. These findings suggest a role for stavudine-related fat distribution changes (ie, lipoatrophy) in the pathogenesis of hypertension in HIV-1-infected patients. This hypothesis was further supported by the observation that the association between prior stavudine exposure and hypertension was no longer present after excluding patients who were ART experienced prior to cART initiation. Pretreated individuals had been exposed to stavudine for longer, possibly continuing the use of stavudine, even while experiencing toxicity and side effects, due to a lack of alternative treatment options before protease inhibitors and nonnucleoside reverse transcriptase inhibitors became available. Though other factors might also play a role in pretreated individuals, it is likely that these individuals experienced more severe lipoatrophy, which may have contributed to their increased risk of hypertension.

To our knowledge, this is the first study showing that the prevalence of hypertension is higher among a contemporary cohort of HIV-1-infected individuals with largely longstanding suppressed viremia and substantial CD4 cell recovery on cART, than among HIV-uninfected controls who are highly comparable regarding demographics, lifestyle, and risk behavior, while adjusting for several potential confounders. The high prevalence rate of hypertension observed in our study compared to those previously reported is likely caused by the



higher age of our study population (median age, 52.7 years vs 40–48 years in earlier studies) [1–9, 20–27]. A previous cohort study showed that HIV-infected patients exposed to cART for >2 years had an increased prevalence of systolic hypertension compared with HIV-uninfected controls, taking into account several potential confounders [6]. The effect of waist-to-hip ratio or prior exposure to particular antiretrovirals other than protease inhibitors was not explored in that study.

Our results suggest a role for both abdominal fat accumulation and peripheral lipoatrophy in the pathophysiology of hypertension in the context of HIV. Whether abdominal obesity and HIV-associated lipohypertrophy share a common pathway in the development of hypertension is unclear. In the general population there is extensive evidence for the link between abdominal obesity and hypertension [28, 29]. Activation of the renin-angiotensin system and sympathetic nervous system has been proposed as a major contributor to the development of hypertension in obese individuals [30]. Activation of the renin-angiotensin system has also been observed among HIV-infected individuals, in particular among those with high visceral adipose tissue [31]. Moreover, Boccarda et al showed in an *in vitro* study that protease inhibitors induced adipocyte dysfunction, and that treatment of adipocytes with protease inhibitors was associated with activation of the adipocyte renin-angiotensin system [32]. These studies suggest the possible involvement of the renin-angiotensin system in the pathophysiology of hypertension in the context of HIV infection, and may explain the association between lipodystrophy and hypertension. However, other hypotheses to explain this link have also been suggested. It has, for instance, been proposed that increased sympathetic nervous system activity might be involved in the pathophysiology of subcutaneous fat loss in HIV-associated adipose redistribution syndrome [33]. This could be relevant in explaining the increased risk of hypertension in the context of HIV infection; however, evidence of increased activity of the sympathetic nervous system in lipodystrophy is scarce [34]. Furthermore, a decline in adiponectin, a hormone secreted by adipose tissue known for its cardioprotective, anti-inflammatory, and antidiabetic characteristics [35], has been associated with both lipodystrophy [36–39] and hypertension [40–42]. Although the exact underlying pathophysiology remains unclear, the association between lipodystrophy and hypertension has been described in various studies [2, 4, 43–45].

Previous research has shown that the immune system might also contribute to the development of hypertension, in part through T-cell activation and production of cytokines, which promotes sodium and water retention in the kidney, and vasoconstriction and remodeling in the vasculature [46]. Inflammation markers have been associated with hypertension in the general population [47–49]. One study, conducted among viremic immunodeficient HIV-infected individuals who were not on cART, suggested that immune activation and microbial

translocation might contribute to later blood pressure increments and the development of hypertension [10]. In our study, in which the majority of HIV-1-infected participants had suppressed viremia and had experienced substantial CD4 cell recovery on treatment, several markers of innate immune activation, microbial translocation, and systemic inflammation were still increased compared to the control group but not associated with hypertension in HIV-1-infected and -uninfected individuals.

Unlike several previous studies [7, 12, 50], we did not find an association between hypertension and nadir CD4 cell count. This discrepancy might be explained by more severe ongoing immune activation and inflammation, or metabolic alterations resulting in an increase in body weight shortly after cART initiation among previously studied HIV-infected populations. Besides, a survivor effect in our cohort could play a role. Other studies support our findings [4, 51]. The role of past immunodeficiency in the development of hypertension remains controversial and needs further study.

Our study has a number of limitations, including that the results of this cross-sectional analysis are mere associations that do not prove direct causal relationships. Besides, presence of unmeasured confounders, which potentially may have influenced our results, cannot be excluded. When interpreting our results, one should take into account that our blood pressure measurements were carried out at a single clinic visit, which might have resulted in an overestimation of the true prevalence of hypertension. Ideally, repeated or ambulatory blood pressure measurements should be carried out to account for the variability in blood pressure [52]. However, it seems unlikely that this potential overestimation would have affected the difference in hypertension prevalence between HIV-1-infected individuals and controls, nor the analysis of determinants of hypertension. Last, in the interpretation of our results we used waist-to-hip ratio as a proxy of visceral fat accumulation and peripheral fat loss, to study the role of abdominal obesity and peripheral lipoatrophy as risk factors for hypertension among HIV-1-infected individuals. Because hip circumference is not a validated surrogate marker for peripheral lipoatrophy, our results should be interpreted with caution. Estimates of body fat distribution would have been more accurate when measured by imaging techniques such as whole body dual-energy X-ray absorptiometry and abdominal computed tomography or magnetic resonance imaging. Unfortunately, such data were not available in our study. Strengths of this study are the relatively large sample size, the enrollment of a highly comparable HIV-uninfected control group, and the availability of detailed data on a wide range of possible confounders and mediators.

We believe that our results are generalizable to other high-income settings with HIV epidemics driven by white men who have sex with men. However, as our cohort includes relatively few women and people of African descent, the extent

to which our results can be generalized to other populations, such as populations in sub-Saharan Africa, remains to be determined.

## CONCLUSIONS

Hypertension is highly prevalent among predominantly virologically suppressed HIV-1-infected individuals. Unfavorable changes in body composition—that is, abdominal obesity among all HIV-1-infected individuals and lipoatrophy among those with prior exposure to stavudine—may contribute to the pathogenesis of the increased risk of hypertension among HIV-1-infected individuals. The contribution of lipoatrophy to the pathogenesis of hypertension may be expected to be largely absent in patients who initiated treatment with more contemporary cART regimens, which should no longer include stavudine. Yet, this might not be the case for HIV-1-infected patients in developing countries, where stavudine is still widely used because of cost considerations. Contemporary regimens may, however, continue to contribute to abdominal obesity. Hence, our results underline the importance of avoiding stavudine as well as limiting the occurrence of abdominal obesity in preventing and managing hypertension and cardiovascular risk among HIV-1-infected patients.

## Supplementary Data

Supplementary materials are available at <http://cid.oxfordjournals.org>. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

## Notes

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