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Signature: Jared Eckman

Date: 4/2/24

Sex Differences in the Prevalence of Age-Related
Hypertension and Diabetes Among Persons with HIV in West Africa

By

Jared Avery Eckman

Master of Science

Clinical Research

Dr. Igbo Ofotokun

Advisor

Dr. Amita Manatunga

Committee Member

Dr. Caitlin Moran

Committee Member

Accepted:

Kimberly Jacob Arriola, Ph.D, MPH

Dean of the James T. Laney School of Graduate Studies

Date

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By

Jared Eckman

B.A., Vanderbilt University, 2018

Advisor: Igho Ofotokun, MD, MSc

Co-Mentor: Lauren Collins, MD, MSc

Co-Mentor: Christina Mehta, PhD, MSPH

**An abstract of a thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
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Abstract

Sex Differences in the Prevalence of Age-Related Hypertension and Diabetes Among Persons with HIV in West Africa

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BACKGROUND: Globally, persons with HIV are living longer and thus experiencing aging-related comorbidities such as hypertension (HTN) and type 2 diabetes (DM). While the epidemiologic burden of these conditions is well characterized in resource-rich settings, data from resource-limited settings, and on the potential for sex differences, are sparse.

METHODS: We leveraged longitudinal data from the International epidemiology Databases to Evaluate AIDS (IeDEA) in West Africa to estimate the prevalence of HTN and DM among PLWH initiating ART. Participants were followed across six HIV clinics in Burkina Faso, Côte d'Ivoire, and Nigeria from 2004-2022. HTN and DM were defined as two interval measurements of systolic and/or diastolic blood pressure $>140/90$ mmHg and fasting blood sugar >126 mg/dL, respectively, at most recent follow-up. PLWH without available outcomes data were excluded from respective analyses. Logistic regression models examined the effects of sex and age, and their combined effect, on each comorbidity.

RESULTS: Among 40,553 PWH (68% female), mean age was 44.6 ± 10.6 years. The majority (74%) had virologic suppression (viral load < 200 copies/mL) and mean CD4 count was 497 ± 315 cells/mm³. The overall prevalence of HTN and DM was 47.4% (95% CI: 46.8%, 48.0%) and 4.7% (95% CI: 4.4%, 5.0%), respectively. These rates increased with age and were significantly higher for men than women overall. When stratified by age category, men had significantly higher odds of DM compared to women in all age categories, with the greatest effect among those younger than 40. Men additionally had significantly higher odds of HTN in each age category. Sex and age were found to have a significant interaction for prevalent hypertension but not for prevalent diabetes.

CONCLUSIONS: Men living with HIV in West Africa experience a higher rate of HTN and DM compared to women living with HIV. The higher burden in men compared with women is intriguing and contrary to previous reports from higher income countries, but deserves further analysis that takes into account potential confounders. These findings highlight the need for more aggressive screening and treatment strategies for PLWH in resource limited settings, potentially differentially by sex.

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INTRODUCTION

HIV as a Major Threat to Public Health Worldwide

Despite significant advances in HIV prevention and therapeutics, the HIV/AIDS epidemic remains a global public health threat with an estimated 1.5 million new cases yearly and nearly 40 million persons living with HIV (PLWH) worldwide.¹ Sub-Saharan Africa continues to have the heaviest burden of global cases, with an estimated 25.3 million in 2020. Despite the persistent rise in global cases, and a failure to meet the UNAID goal of treating 90% of PLWH, the number of people accessing antiretroviral therapy (ART) has improved over time, from 7.8 million in 2010 to 29.8 million by the end of 2022. In Western and Central Africa alone, 3.5 of the 4.7 million PLWH accessed treatment in 2020.¹

Non-AIDS Comorbidities

Increased access to ART, including via the World Health Organization's "Treat All" recommendation to initiate ART for all PLWH, has led to a significant reduction in AIDS-related morbidity and mortality.^{2,3,4} Non-AIDS comorbidities (NACM) are now driving morbidity and mortality among PLWH. Access to effective ART has dramatically improved the lifespan of PLWH, leading to aging-related causes of morbidity in this population.^{5,6,7} A large United States (U.S.) cohort study among PLWH with access to care demonstrated that from 2000-2003 to 2014-2016, the overall life expectancy at 21 years of age improved by 18.4 years.⁸ Nonetheless, the life expectancy years gained are not comorbidity-free, such that PLWH lived 16.3 fewer healthy years.⁹

The prevalence of several NACM, including hypertension (HTN) and diabetes mellitus type 2 (DM), have significantly increased among PLWH over time, surpassing the prevalence

observed in the general population.^{10,11} Further, increasing NACM risk in HIV has been shown to contribute to the lifespan discrepancy among people living with and without HIV that persists even into the modern ART era. Compared with persons without HIV, the higher prevalence and overall burden of NACM in PLWH is likely multifactorial, including toxicities associated with long-term ART use, higher rates of traditional risk factors in PLWH such as tobacco and recreational drug use, and HIV-related chronic inflammation and immune activation that has been associated with accelerated immunosenescence (the progressive decline of the immune system due to natural aging effects) among PLWH.^{12,13,14,15} This shift from AIDS-related illness and death to aging-related NACM among PLWH has important implications for the long-term management of HIV, including optimization of NACM prevention and screening strategies for PLWH specifically. HTN and DM represent two NACM of particular importance given their high prevalence and implications for morbidity.

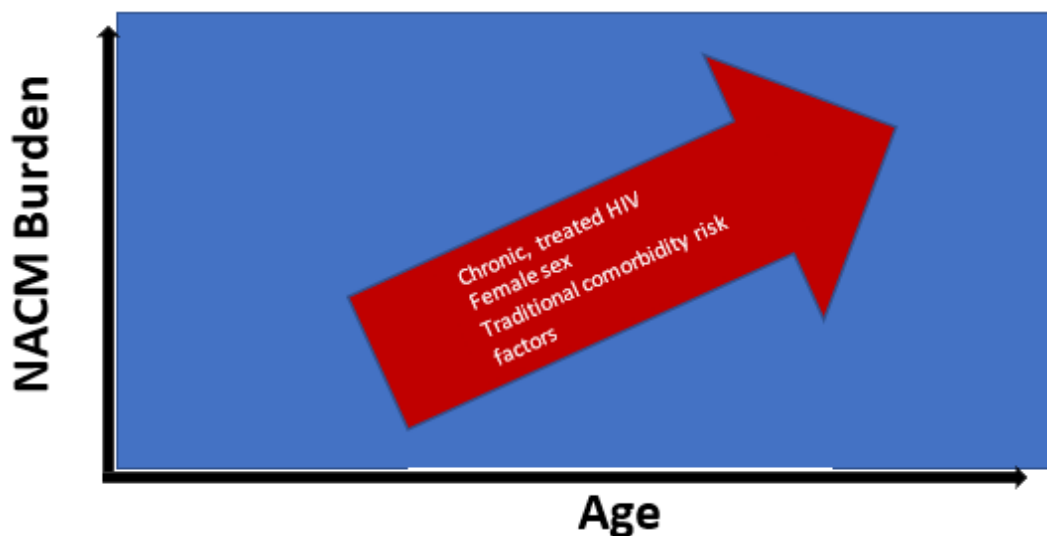
Aging with HIV

Aging is consistently associated with the development of NACM in PLWH. While the increase in NACM has been demonstrated across PLWH, older individuals compared with younger appear to be disproportionately impacted.¹⁶ HIV seems to promote premature senescence, a likely contributor to the high prevalence of NACM in PLWH, and the increased lifespan of PLWH further compounds the risks of premature aging. Some have pointed to a process of chronic low-grade inflammation in PLWH, called “inflammaging”, that may promote this premature loss of physiologic function. HIV and aging appear to share other pathologic processes, including mitochondrial dysfunction and aberrant production of reactive oxygen species (ROS).^{12,13} Investigating the effects of aging on the development of NACM across populations will further elucidate mechanisms underpinning these findings.

Sex Differences in NACM Risk

Despite comprising more than half of PLWH globally, women living with HIV remain critically understudied. Studies have suggested a higher risk of several NACM, including HTN and DM, among women compared with men.¹⁷ Research by our group leveraging the largest and longest U.S. HIV cohort has demonstrated a higher overall burden of NACM among women with versus without HIV.^{18,19} Additionally, among PLWH in the U.S., women compared to men experience a higher overall NACM burden.²⁰ Several explanations for this discrepancy have been put forward, including physiologic changes during the menopausal transition, increased immune activation seen in women in response to HIV-1, and structural and sociobehavioral factors that hinder access to healthcare for women.^{21,22,23,24 25} The current paradigm considers chronic, treated HIV as a risk factor for the development of aging-related NACM with a potential greater risk among women (Figure 1).

FIGURE 1. PARADIGM OF NACM BURDEN



NACM Epidemiology in Sub-Saharan Africa

While the epidemiologic burden of these comorbidities is well characterized in resource-rich settings, data from resource-limited settings are sparse. This is of particular importance in sub-Saharan Africa, which continues to bear the brunt of the epidemic with more than two-thirds of the global burden of HIV cases.²⁶ Data thus far have shown conflicting trends in NACM between various global regions, including data showing decreased rates of hypertension among PLWH in sub-Saharan Africa^{27,28} in addition to studies showing an elevated risk in Central Africa.²⁹ Additionally, a recent study on the relationship between HIV serostatus and cardiovascular disease in sub-Saharan Africa indicated that PLWH in Namibia were less likely to have self-reported diabetes, while adjusted data from Lesotho showed no association between self-reported diabetes and HIV serostatus.³⁰ This discordance and variability across countries highlights a critical gap in the literature in evaluating NACM in sub-Saharan Africa. Given greater access to life-saving ART, the clinical care needs of PLWH are rapidly evolving, and this aging experience among PLWH in sub-Saharan Africa remains largely uncharacterized.³¹

Specific Aims

The following specific aims guided the execution of the thesis project:

SA1: To estimate the prevalence of hypertension and diabetes mellitus among PLWH in West Africa

SA2: To assess the association of age and sex with the prevalence of hypertension and diabetes mellitus, independently and synergistically, among PLWH in West Africa

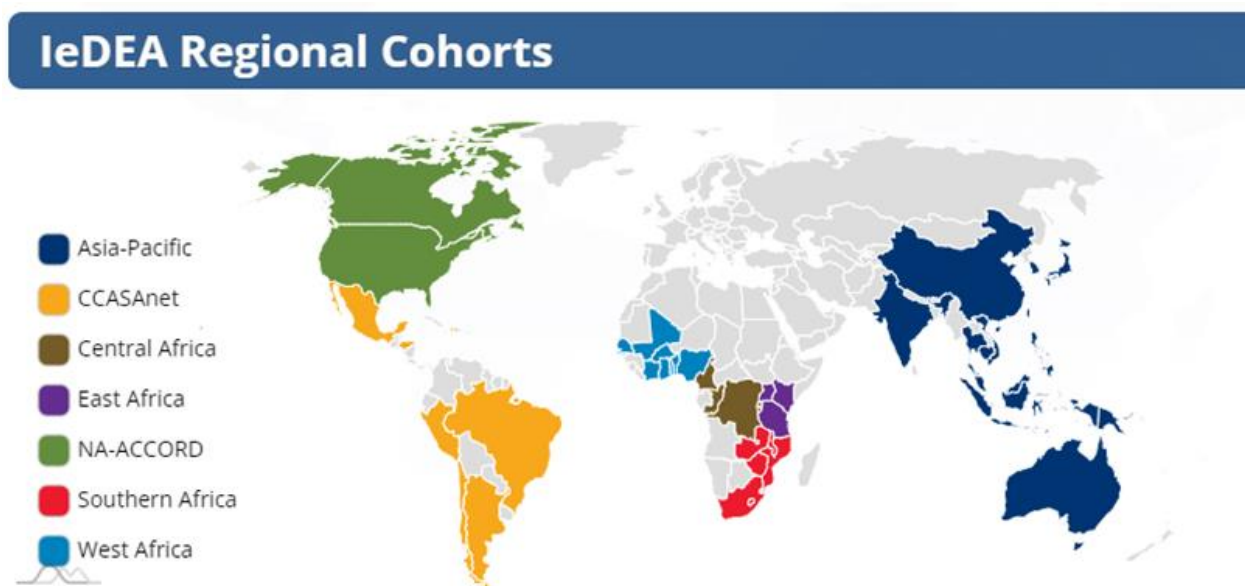
Hypothesis: Both increased age and female sex, separately and synergistically, are associated with increased prevalence of hypertension and diabetes in this cohort.

METHODS

West Africa IeDEA Cohort

The International epidemiology Databases to Evaluate AIDS (IeDEA) is a large cohort with seven regional data centers across the globe (Figure 2). The West Africa cohort, one of the seven global branches, was established by the National Institute of Allergy and Infectious Diseases (NIAID) in 2006 and is now in its fourth renewal (2021-2026). Participating countries include Cote d'Ivoire, Burkina Faso, Togo, and Nigeria. Six participating clinics are located in the cities of Abidjan, Bobo Dioulasso, Lomé, and Lagos (Figure 3). The sub-regional data hub is in Abidjan, Cote d'Ivoire, and the regional data center responsible for collecting and merging the data across the West Africa centers is located in Bordeaux, France. Data are collected from affiliated cohorts in the regional data center every 24 months. Data collection begins when patients initiate ART and clinical visits are initially monthly or bimonthly, before occurring every 2-3 months once treatment is stabilized.³² The principal investigators for this cohort are Drs. Igbo Ofotokun (Emory University), Antoine Jaquet (University of Bordeaux), and Didier Ekouevi (University of Lomé).

Upon enrollment in the cohort, patient follow-up reflects the standards of care in the participating clinics. Patients are consecutively included in the cohort as they begin anti-retroviral therapy. Those who were already being followed at participating clinics had their data collected retrospectively in addition to prospective data collection. Those who enrolled following the beginning of the cohort had their data prospectively collected.

FIGURE 2. IeDEA REGIONAL COHORTS**FIGURE 3. WEST AFRICA COHORT**

Acquisition of Data

To access the data, a concept sheet outlining the research proposal was submitted to the IeDEA West Africa Executive Council. Upon acceptance, the data were then received from the regional data center in Bordeaux, France. Subsequent data management, data cleaning, and analysis were performed by our research team at Emory University.

Inclusion and exclusion criteria

Data from all participants ≥ 18 years old enrolled in the W. Africa cohort were included in the analysis. Participants without available outcomes data were excluded from respective analyses.

Study Design

This is a cross-sectional study with secondary data analysis extracted from a longitudinal cohort.

Outcome Measures

HTN was defined as two measurements of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. DM was defined as at least two recorded values of fasting blood glucose ≥ 126 mg/dL. The two measurements could not be greater than two years apart to qualify as a case. Data on HbA1C the use of antihypertensives or antidiabetic agents were not available for classification of cases.

Statistical methods

T-tests were used to compare continuous participant characteristics across men and women, while Fisher's exact or Chi-square tests were used to compare rates across men and women.

Logistic regression models examined the effects of sex and age (as a three-level categorical variable), and their combined effect, on each comorbidity. Age was divided into the following categories: < 40 years old, 40-49 years old, and ≥ 50 years old. These categories were selected based on categories used in prior research and the age distribution in the cohort.

An adjusted model included BMI at most recent measurement and lagged CD4 count as covariates. The lagged CD4 count used the last available value. An additional model included the clinical center as a covariate.

TABLE 1. OUTCOME DEFINITIONS		
Outcome	Definition	Source
HTN	Systolic blood pressure ≥ 140 mmHg OR Diastolic blood pressure ≥ 90 mmHg	Clinical measurement
DM	Fasting blood glucose of ≥ 126 mg/dL	Laboratory measurement

RESULTS

Study Population

All participants in the cohort were at least 18 years old, living with HIV, and initiated on ART upon enrollment. Enrollment years ranged from 1992 to 2022, with a median enrollment year of 2010. Years of clinic visits from which the data were extracted ranged from 2004 to 2022, with a median enrollment year of 2020.

A total of 40,553 participants were included in the analysis, of whom 13,103 were men and 27,450 were women. 42.8% of participants lived in Abidjan, 40.0% in Lagos, 15.9% in Bobo Dioulasso, and 1.3% in Lomé. Among the participating clinics, the Nigerian Institute for Medical

Research (NIMR) in Lagos contributed the highest percentage of participants in the cohort with 40.0% (Table 2). Other participating clinics included Espoir-Vie Togo (EVT) in Lomé with 1.3% of participants, Centre National de Transfusion Sanguine (CNTS) in Abidjan with 10.7%, Centre Intégré de Recherches Biocliniques d'Abidjan (CIRBA) with 10.8%, Centre de Prise en Charge et de Formation (CEPREF) in Abidjan with 21.3%, and BOBO in Bobo Dioulasso with 15.9%.

TABLE 2. DISTRIBUTION OF PARTICIPANTS BY CLINICAL CENTER

Center*	Overall (40,553)	Men (13,103)	Women (27,450)	P-value**
NIMR	16223/40553 (40.0%)	5499/13103 (42.0%)	10724/27450 (39.1%)	<0.0001
EVT	510/40553 (1.3%)	128/13103 (1.0%)	382/27450 (1.4%)	
CNTS	4349/40553 (10.7%)	1619/13103 (12.4%)	2730/27450 (9.9%)	
CIRBA	4377/40553 (10.8%)	1801/13103 (13.7%)	2576/27450 (9.4%)	
CEPREF	8630/40553 (21.3%)	2246/13103 (17.1%)	6384/27450 (23.3%)	
BOBO	6464/40553 (15.9%)	1810/13103 (13.8%)	4654/27450 (17.0%)	

*NIMR: Nigerian Institute for Medical Research (NIMR) in Lagos

EVT: Espoir-Vie Togo in Lomé

CNTS: Centre National de Transfusion Sanguine in Abidjan

CIRBA: Centre Intégré de Recherches Biocliniques d'Abidjan

CEPREF: Centre de Prise en Charge et de Formation in Abidjan

BOBO: Bobo Dioulasso

**P-value was calculated using a T-Test

Baseline Characteristics

Overall, participants in the cohort had a mean age \pm standard deviation (SD) of 44.6 ± 10.6 years old (Table 1). Men had a mean age of 48.3 ± 10.4 years old, while women had a mean age of 42.9 ± 10.3 . The average systolic blood pressure at last visit month was 115.4 ± 28.7 mmHg for the cohort as a whole, with an average of 118.2 ± 30.7 among men and 114.0 ± 27.6 among women. The average diastolic pressure at last visit month for the entire cohort was 83.5 ± 19.8 , with an average of 85.6 ± 20.3 among men and 82.4 ± 19.5 among women. The fasting blood glucose, had an overall mean of 94.6 ± 26.7 mg/dL. Men had an average fasting blood glucose of 97.3 ± 29.4 and women had an average of 93.3 ± 25.3 .

All participants were prescribed ART when enrolled in the study, and 90.8% of all participants were ART-naïve upon enrollment. The median last CD4 count for all participants was 469 cells/mm³, with an average count of 391.0 among men and 511.0 among women. With viral suppression defined as a viral load of less than 200 copies per millimeter, 73.7% of all participants were virally suppressed. 70.5% of the men in cohort were virally suppressed at their most recent clinic visit compared to 75.2% of the women.

Using a t-test, Chi-square test, or Fisher's exact test as appropriate, all reported baseline characteristics were significantly different ($p < 0.0001$) between men and women.

TABLE 3. BASELINE CHARACTERISTICS OF PARTICIPANTS

Characteristic	Overall (n=40,553)	Men (n=13,103)	Women (n=27,450)	P-value*
Age at Last Visit (years)				
Mean \pm SD	44.6 \pm 10.6	48.3 \pm 10.4	42.9 \pm 10.3	<0.0001
Average Systolic BP at Last Visit Month (mmHg)				
Mean \pm SD (N)	115.4 \pm 28.7 (19068)	118.2 \pm 30.7 (6296)	114.0 \pm 27.6 (12772)	<0.0001
Average Diastolic BP at Last Visit Month (mmHg)				
Mean \pm SD (N)	83.5 \pm 19.8 (18963)	85.6 \pm 20.3 (6266)	82.4 \pm 19.5 (12697)	<0.0001
Average Fasting Blood Glucose at Last Visit Month (mg/dL)				
Mean \pm SD (N)	94.6 \pm 26.7 (6250)	97.3 \pm 29.4 (2008)	93.3 \pm 25.3 (4242)	<0.0001
BMI at Last Visit Month (kg/m²)				
Mean \pm SD (N)	25.1 \pm 11.3 (20356)	24.0 \pm 11.3 (6824)	25.6 \pm 11.2 (13532)	<0.0001
Is the patient ART-naïve upon enrollment?				
Yes	34732/38236 (90.8%)	11185/12174 (91.9%)	23547/26062 (90.3%)	<0.0001
No	3504/38236 (9.2%)	989/12174 (8.1%)	2515/26062 (9.7%)	
Last CD4 count (cells/mm³)				
Median[Q1-Q3]	469.0[260.0 - 690.0]	391.0[208.0 - 588.5]	511.0[293.0 - 733.0]	<0.0001
Categorical Last CD4 count (cells/mm³)				
last CD4 \geq 500	18301/39654 (46.2%)	4511/12835 (35.1%)	13790/26819 (51.4%)	<0.0001
last CD4 between 200-499	13975/39654 (35.2%)	5238/12835 (40.8%)	8737/26819 (32.6%)	
last CD4 < 200	7378/39654 (18.6%)	3086/12835 (24.0%)	4292/26819 (16.0%)	
Last RNA <200 (copies/mL)				
Yes	24345/33035 (73.7%)	7458/10578 (70.5%)	16887/22457 (75.2%)	<0.0001
No	8690/33035 (26.3%)	3120/10578 (29.5%)	5570/22457 (24.8%)	

*P-values were calculated using T-Test or Fisher's exact or Chi-square test

Prevalence of Hypertension and Diabetes

The overall prevalence of hypertension in the cohort was 47.4%, with a prevalence of 55.2% among men and 43.6% among women ($p < 0.0001$) (Table 4). The prevalence of hypertension was stratified by age as a three-level categorical variable and increased with each successive age category ($p < 0.0001$). Men compared to women had a statistically significantly higher prevalence of hypertension for the younger than 40 years old ($p < 0.0001$) and at least 50 years old age groups ($p < 0.0001$), while there was no significant difference in the 40-49 age group ($p = 0.73$).

For diabetes, the overall prevalence in the cohort was 4.7% (Table 4), while men compared to women had a significantly higher prevalence at 7.3% compared to 3.6% ($p < 0.0001$). The prevalence of diabetes increased with each successive age category, and men had a significantly higher prevalence compared to women within each age category.

TABLE 4. PREVALENCE OF HYPERTENSIONS AND DIABETES OVERALL AND STRATIFIED BY SEX AND AGE AMONG WEST AFRICAN PERSONS WITH HIV

Age, years	Overall	Men	Women	p-value*
Hypertension				
Overall	13018/27483 (47.4%)	4983/9033 (55.2%)	8035/18450 (43.6%)	<0.0001
<40	2518/9967 (25.3%)	594/2034 (29.2%)	1924/7933 (24.3%)	<0.0001
40-49	5006/9682 (51.7%)	1661/3228 (51.5%)	3345/6454 (51.8%)	0.73
≥50	5494/7834 (70.1%)	2728/3771 (72.3%)	2766/4063 (68.1%)	<0.0001
Type 2 Diabetes				
Overall	897/19166 (4.7%)	421/5774 (7.3%)	476/13392 (3.6%)	<0.0001
<40	55/5102 (1.1%)	15/853 (1.8%)	40/4249 (0.9%)	0.035
40-49	230/6980 (3.3%)	80/1882 (4.3%)	150/5098 (2.9%)	0.007
≥50	612/7084 (8.6%)	326/3039 (10.7%)	286/4045 (7.1%)	<0.0001

Data are presented as no. (%).

* P-values are reported using a Chi-square test.

Regression Models with HTN as Outcome

Several logistic regression models were used to estimate the effects of sex and age on the odds of prevalent HTN (Table 5A). In a partially adjusted model, which included categorical age, sex, and an interaction term between age and sex, women had 0.86 times the odds of hypertension compared to men (95% CI: 0.82, 0.91). This effect was strengthened in the two adjusted models. The first adjusted model included the additional covariates of BMI and CD4 count, while the second included these covariates in addition to clinical center. In the cohort overall, those in higher age categories had a significantly higher odds of hypertension compared to those younger than 40 years old. This effect held true in all three models.

Men compared to women had a significantly higher odds of hypertension in the adjusted models. Among those younger than 40 years old, and after controlling for BMI, CD4 count, and clinical center, men had 1.45 times the odds of hypertension compared to women (95% CI: 1.25, 1.68). Among those in the 40-49 age group, there was no significant effect of sex in the unadjusted model, but in both adjusted models men had significantly higher odds of prevalent hypertension. In the age group with those at least 50 years old, men had 1.49 times the odds of hypertension compared to women in the fully adjusted model (95% CI: 1.30, 1.71).

In the adjusted model that included BMI and CD4 count as covariates, sex ($p < 0.0001$), age ($p < 0.0001$), and sex*age interaction ($p = 0.019$) were significantly associated with prevalent hypertension.

TABLE 5A. ODDS OF HYPERTENSION BY SEX AND AGE AMONG WEST AFRICAN PERSONS WITH HIV

Predictor	Odds ratio for unadjusted model (95% CI) *	Odds ratio for model 1 (95%CI)**	Odds ratio for model 2 (95%CI)***
Female sex			
Age 40-49	3.36 (3.13, 3.607)	3.081 (2.816, 3.372)	3.306 (2.998, 3.646)
Age >50	6.661 (6.126, 7.241)	6.116 (5.484, 6.821)	7.277 (6.466, 8.19)
REF <40	-	-	
Male sex			
Age 40-49	2.57 (2.284, 2.891)	2.438 (2.107, 2.822)	2.89 (2.461, 3.393)
Age >50	6.341 (5.628, 7.144)	5.685 (4.893, 6.607)	7.494 (6.359, 8.831)
REF <40	-	-	
Male vs Female			
Age 40-49	0.9852 (0.9053, 1.0721)	1.3012 (1.1655, 1.4527)	1.2657 (1.1243, 1.4249)
Age >50	1.2264 (1.1129, 1.3516)	1.5283 (1.3413, 1.7415)	1.491 (1.3005, 1.7094)
Age <40	1.2883 (1.1559, 1.4359)	1.6441 (1.4372, 1.8809)	1.4479 (1.2487, 1.6788)
*Unadjusted model by categorical age, sex and interaction between age and sex			
**Adjusted by categorical age, sex interaction between age and sex, BMI and CD4 count			
***Adjusted by categorical age, sex interaction between age and sex, BMI and CD4 count, center			

Regression Models with DM as Outcome

In each regression model, those in higher age categories had significantly higher odds of prevalent DM compared to those younger than 40 years old. (Table 5B). When stratified by age category, men had significantly higher odds of DM compared to women in all age categories, with the greatest effect among those younger than 40. In this age category for model 2, men had 3.14 times the odds of DM compared to women (95% CI: 1.40, 7.07).

In the model adjusted for BMI and CD4 count, sex ($p<0.0001$) and age ($p<0.0001$) were significantly associated with prevalent diabetes. However, the sex*age interaction term was not significant ($p=0.76$).

TABLE 5B. ODDS OF DIABETES BY SEX AND AGE AMONG WEST AFRICAN PERSONS WITH HIV

Predictor	Odds ratio for unadjusted model (95% CI) *	Odds ratio for adjusted model (95%CI)**	Odds ratio for adjusted model (95%CI)***
Female sex			
Age 40-49	3.189 (2.245, 4.53)	2.505 (1.478, 4.248)	2.292 (1.351, 3.888)
Age >50	8.003 (5.732, 11.173)	6.028 (3.655, 9.943)	5.508 (3.339, 9.088)
REF <40	-	-	
Male sex			
Age 40-49	2.48 (1.42, 4.331)	1.852 (0.873, 3.931)	1.654 (0.777, 3.521)
Age >50	6.713 (3.978, 11.329)	4.386 (2.19, 8.781)	3.745 (1.865, 7.521)
REF <40	-	-	
Male vs Female			
Age 40-49	1.4644 (1.1105, 1.9312)	2.0746 (1.3134, 3.2768)	2.2682 (1.4316, 3.5936)
Age >50	1.5793 (1.3374, 1.8651)	2.0415 (1.5081, 2.7636)	2.1367 (1.5747, 2.8991)
Age <40	1.8828 (1.0354, 3.4239)	2.8062 (1.2528, 6.2858)	3.143 (1.3968, 7.0722)
*Unadjusted model by categorical age, sex and interaction between age and sex			
**Adjusted by categorical age, sex interaction between age and sex, BMI and CD4 count			
***Adjusted by categorical age, sex interaction between age and sex, BMI and CD4 count, center			

CONCLUSIONS

Contrary to our initial hypothesis, the results described above suggest that, among PLWH in West Africa, men compared to women experience a higher prevalence of HTN and DM. This conclusion is supported by the higher prevalence of these outcomes among men overall and for each age category, apart from hypertension among those aged 40-49 in which women had a non-significantly higher prevalence (Table 4). Additionally, the regression results generally demonstrated a higher odd of both HTN and DM among men compared to women. Among average age, women had a significantly lower odds of both outcomes in the respective unadjusted and adjusted models (Tables 5A and 5B). This pattern of sex difference was only unsupported in the case of the unadjusted model estimating the odds of HTN in men compared to women (OR: 0.98, 95% CI: 0.91, 1.07).

As hypothesized, the data suggest that increasing age is associated with higher prevalence of both HTN and DM. Each successive age category was found to have a higher prevalence of these conditions, which held true for both men and women (Table 4). The regression results also bare out this pattern. When the effect of age was estimated at the level of each sex, the higher age categories generally carried a higher odd of both HTN and DM. However, in the adjusted models, the odds of diabetes among those 40-49 years old compared to those younger than 40 crossed the null value. In evaluating the interaction term, sex and age were found to have a significant interaction for prevalent hypertension but not for prevalent diabetes.

In addition, the results suggest a high rate of viral suppression among PLWH in West Africa and particularly among women. As shown in Table 3, 73.7% of all participants were virally suppressed, with women having a significantly higher prevalence of viral suppression compared to men ($p < 0.0001$). This is consistent with a higher median CD4 count among women, and a higher proportion of women compared to men who have a CD4 count of at least 500. Together, these data support the conclusion that women living with HIV in West Africa have greater HIV control compared to men.

DISCUSSION

The results herein described are striking for a pattern of sex differences that contradicts those seen in North American populations. Several causes may explain this contrast. First, it is critical to recognize that, in the general population, men experience a higher rate of hypertension and diabetes compared to women.^{33,34} The results of this study are therefore consistent with the general epidemiologic pattern. In addition, the median age of the North American cohort cited above was 50 years old compared to a mean age of 44.6 years old in the IeDEA West Africa

cohort.²⁰ The younger age in the latter cohort may translate to fewer women who have entered menopause, which is believed to contribute to the sex differences previously observed. The data also suggest a high degree of viral suppression among PLWH in West Africa, particularly among women. This may result in reduced viremia and chronic inflammation which in turn could contribute to lower prevalence of HTN and DM.^{12,13}

The prevalence of HTN and DM estimated in this study are generally in line with the published literature. A cross-sectional study in Burkina Faso found a prevalence of HTN among PLWH of 39.8% and a prevalence of diabetes of 7.3%, compared to 47.4% and 4.7%, respectively, in this study.³⁵ In addition, a systematic review and meta-analysis reported a prevalence of diabetes of 5.1% (95% CI: 4.3-5.9) among PLWH in Africa, although this study was not restricted to West Africa.³⁶

Strengths and Limitations

The major strength of this study is the large dataset consisting of 40,553 participants across four countries and six clinical centers. The setting of West Africa is also a major strength, as this is an understudied region and a missing component of the current literature on aging with HIV. In addition, these participants were followed over several years and the extracted data provide a wide window of time. The data analyzed in this study also reflected routine care and real-world data, as each clinic adhered to its own standards for clinical care and did not follow a prescribed protocol.

A limitation of the study lies in the incomplete medication data, which led to several weaknesses. Without a complete medication history for each participant, we were unable to account for cases of HTN and DM that were well-controlled on medication and would not register on recent clinical visits. Therefore, it is possible these results underestimated the true

number of cases of HTN and DM. In addition, without sufficient medication data, we were unable to control for ART exposure. Since different classes of ART predispose to cardiovascular and metabolic disease in varying degrees, both class and duration of ART would be important covariates to capture and control for.

The dataset also contained incomplete and unreliable information for tobacco use, alcohol use, and pregnancy history. These covariates can each significantly impact one's risk for HTN and DM and must be controlled for in future studies. A history of pregnancy could also lead to more contact with the healthcare system, which may in turn lead to prevention and/or treatment of conditions such as HTN and DM. In addition, the heterogeneity in breadth and frequency of clinical follow-up exposes participants to varying conditions.

Future Directions

Further work in this area will analytically compare prevalence of HTN and DM among PLWH between West African countries and clinics to refine our understanding of the epidemiology of the region. We will also determine which clinical centers have the most reliable and robust data and estimate the prevalence of additional NACM at these sites. In addition, we will perform analytic comparisons of NACM burden among PLWH in West Africa and North America. This will shine further light on the contrast in sex differences between these two regions and help elucidate drivers of these opposing patterns.

REFERENCES

¹ https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

² Johnson LF, Anderegg N, Zaniwski E, et al. Global variations in mortality in adults after initiating antiretroviral treatment: an updated analysis of the International epidemiology Databases to Evaluate AIDS cohort collaboration. *AIDS*. 2019;33 Suppl 3(Suppl 3):S283-S294. doi:10.1097/QAD.0000000000002358

-
- ³ World Health Organization Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. 2016. Available at: <http://www.who.int/hiv/pub/arv/arv-2016/en/>
 - ⁴ Tymejczyk O, Brazier E, Yiannoutsos CT, et al.. Changes in rapid HIV treatment initiation after national "treat all" policy adoption in 6 sub-Saharan African countries: Regression discontinuity analysis. *PLoS Med* 2019;16:e1002822. doi: 10.1371/journal.pmed.1002822.
 - ⁵ Trickey A, May MT, Vehreschild J, et al. Cause-Specific Mortality in HIV-Positive Patients Who Survived Ten Years after Starting Antiretroviral Therapy. *PLoS One*. 2016;11(8):e0160460. Published 2016 Aug 15. doi:10.1371/journal.pone.0160460
 - ⁶ Gallant J, Hsue PY, Shreay S, Meyer N. Comorbidities Among US Patients With Prevalent HIV Infection-A Trend Analysis. *J Infect Dis*. 2017 Dec 19;216(12):1525-1533. doi: 10.1093/infdis/jix518. PMID: 29253205.
 - ⁷ Cole MB, Galárraga O, Rahman M, Wilson IB. Trends in Comorbid Conditions Among Medicaid Enrollees With HIV. *Open Forum Infect Dis*. 2019 Mar 10;6(4):ofz124. doi: 10.1093/ofid/ofz124. PMID: 30976608; PMCID: PMC6453520.
 - ⁸ Marcus JL, Leyden WA, Alexeeff SE, Anderson AN, Hechter RC, Hu H, Lam JO, Towner WJ, Yuan Q, Horberg MA, Silverberg MJ. Comparison of Overall and Comorbidity-Free Life Expectancy Between Insured Adults With and Without HIV Infection, 2000-2016. *JAMA Netw Open*. 2020 Jun 1;3(6):e207954. doi: 10.1001/jamanetworkopen.2020.7954. PMID: 32539152; PMCID: PMC7296391.
 - ⁹ Collins LF, Armstrong WS. What It Means to Age With HIV Infection: Years Gained Are Not Comorbidity Free. *JAMA Netw Open*. 2020 Jun 1;3(6):e208023. doi: 10.1001/jamanetworkopen.2020.8023. PMID: 32539147.
 - ¹⁰ Schouten J, Wit FW, Stolte IG, Kootstra NA, van der Valk M, Geerlings SE, Prins M, Reiss P; AGEHIV Cohort Study Group. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEHIV cohort study. *Clin Infect Dis*. 2014 Dec 15;59(12):1787-97. doi: 10.1093/cid/ciu701. Epub 2014 Sep 2. PMID: 25182245.
 - ¹¹ Davis K, Perez-Guzman P, Hoyer A, Brinks R, Gregg E, Althoff KN, Justice AC, Reiss P, Gregson S, Smit M. Association between HIV infection and hypertension: a global systematic review and meta-analysis of cross-sectional studies. *BMC Med*. 2021 May 13;19(1):105. doi: 10.1186/s12916-021-01978-7. Erratum in: *BMC Med*. 2021 Sep 8;19(1):228. PMID: 33980222; PMCID: PMC8117497.
 - ¹² Caron M, Auclair M, Vissian A, Vigouroux C, Capeau J. Contribution of mitochondrial dysfunction and oxidative stress to cellular premature senescence induced by antiretroviral thymidine analogues. *Antivir Ther*. 2008;13(1):27-38. PMID: 18389896.
 - ¹³ Chen YF, Stampley JE, Irving BA, Dugas TR. Chronic Nucleoside Reverse Transcriptase Inhibitors Disrupt Mitochondrial Homeostasis and Promote Premature Endothelial Senescence. *Toxicol Sci*. 2019 Dec 1;172(2):445-456. doi: 10.1093/toxsci/kfz203. Erratum in: *Toxicol Sci*. 2021 Sep 28;183(2):415. PMID: 31545371.
 - ¹⁴ Appay V, Almeida JR, Sauce D, Autran B, Papagno L. Accelerated immune senescence and HIV-1 infection. *Exp Gerontol*. 2007 May;42(5):432-7. doi: 10.1016/j.exger.2006.12.003. Epub 2007 Jan 8. PMID: 17307327.
 - ¹⁵ Lagathu C, Cossarizza A, Béréziat V, Nasi M, Capeau J, Pinti M. Basic science and pathogenesis of ageing with HIV: potential mechanisms and biomarkers. *AIDS*. 2017 Jun 1;31 Suppl 2:S105-S119. doi: 10.1097/QAD.0000000000001441. PMID: 28471941.
 - ¹⁶ Pond RA, Collins LF, Lahiri CD. Sex Differences in Non-AIDS Comorbidities Among People With Human Immunodeficiency Virus. *Open Forum Infect Dis*. 2021 Nov 3;8(12):ofab558. doi: 10.1093/ofid/ofab558. PMID: 34888399; PMCID: PMC8651163
 - ¹⁷ Birabaharan M, Strunk A, Kaelber DC, Smith DM, Martin TCS. Sex differences in type 2 diabetes mellitus prevalence among persons with HIV. *AIDS*. 2022 Mar 1;36(3):383-389. doi: 10.1097/QAD.0000000000003127. PMID: 34750292; PMCID: PMC8795484.
 - ¹⁸ Collins LF, Sheth AN, Mehta CC, Naggie S, Golub ET, Anastos K, French AL, Kassaye S, Taylor T, Fischl MA, Adimora AA, Kempf MC, Palella FJ, Tien PC, Ofotokun I. The Prevalence and Burden of Non-AIDS Comorbidities Among Women Living With or at Risk for Human Immunodeficiency Virus Infection in the United States. *Clin Infect Dis*. 2021 Apr 26;72(8):1301-1311. doi: 10.1093/cid/ciaa204. PMID: 32115628; PMCID: PMC8075036.
 - ¹⁹ Collins LF, Sheth AN, Mehta CC, Naggie S, Golub ET, Anastos K, French AL, Kassaye S, Taylor TN, Fischl MA, Adimora AA, Kempf MC, Palella FJ, Tien PC, Ofotokun I. Incident Non-AIDS Comorbidity Burden Among

Women With or at Risk for Human Immunodeficiency Virus in the United States. *Clin Infect Dis*. 2021 Oct 5;73(7):e2059-e2069. doi: 10.1093/cid/ciaa1928. PMID: 33388773; PMCID: PMC8492222.

²⁰ Collins LF, Palella FJ, Mehta CC, et al. Aging-Related Comorbidity Burden Among Women and Men With or At-Risk for HIV in the US, 2008-2019. *JAMA Netw Open*. 2023;6(8):e2327584.

²¹ Meier A, Chang JJ, Chan ES, Pollard RB, Sidhu HK, Kulkarni S, Wen TF, Lindsay RJ, Orellana L, Mildvan D, Bazner S, Streeck H, Alter G, Lifson JD, Carrington M, Bosch RJ, Robbins GK, Altfeld M. Sex differences in the Toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. *Nat Med*. 2009 Aug;15(8):955-9. doi: 10.1038/nm.2004. Epub 2009 Jul 13. PMID: 19597505; PMCID: PMC2821111.

²² Imai K, Sutton MY, Mdofo R, Del Rio C. HIV and Menopause: A Systematic Review of the Effects of HIV Infection on Age at Menopause and the Effects of Menopause on Response to Antiretroviral Therapy. *Obstet Gynecol Int*. 2013;2013:340309. doi: 10.1155/2013/340309. Epub 2013 Dec 19. PMID: 24454386; PMCID: PMC3880754.

²³ Sohler NL, Li X, Cunningham CO. Gender disparities in HIV health care utilization among the severely disadvantaged: can we determine the reasons? *AIDS Patient Care STDS*. 2009 Sep;23(9):775-83. doi: 10.1089/apc.2009.0041. PMID: 19663745; PMCID: PMC2859765.

²⁴ Palella FJ, Hart R, Armon C, Tedaldi E, Yangco B, Novak R, Battalora L, Ward D, Li J, Buchacz K; HIV Outpatient Study (HOPS). Non-AIDS comorbidity burden differs by sex, race, and insurance type in aging adults in HIV care. *AIDS*. 2019 Dec 1;33(15):2327-2335. doi: 10.1097/QAD.0000000000002349. PMID: 31764098.

²⁵ Moran CA, Collins LF, Beydoun N, Mehta PK, Fatade Y, Isiadinso I, Lewis TT, Weber B, Goldstein J, Ofotokun I, Quyyumi A, Choi MY, Titanji K, Lahiri CD. Cardiovascular Implications of Immune Disorders in Women. *Circ Res*. 2022 Feb 18;130(4):593-610. doi: 10.1161/CIRCRESAHA.121.319877. Epub 2022 Feb 17. PMID: 35175848; PMCID: PMC8869407.

²⁶ Dwyer-Lindgren, L., Cork, M.A., Sligar, A. et al. Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017. *Nature* 570, 189–193 (2019). <https://doi.org/10.1038/s41586-019-1200-9>.

²⁷ Dillon DG, Gurdasani D, Riha J, Ekoru K, Asiki G, Mayanja BN, Levitt NS, Crowther NJ, Nyirenda M, Njelekela M, Ramaiya K, Nyan O, Adewole OO, Anastos K, Azzoni L, Boom WH, Compostella C, Dave JA, Dawood H, Erikstrup C, Fourie CM, Friis H, Kruger A, Idoko JA, Longenecker CT, Mboni S, Mukaya JE, Mutimura E, Ndhlovu CE, Praygod G, Pefura Yone EW, Pujades-Rodriguez M, Range N, Sani MU, Schutte AE, Sliwa K, Tien PC, Vorster EH, Walsh C, Zinyama R, Mashili F, Sobngwi E, Adebamowo C, Kamali A, Seeley J, Young EH, Smeeth L, Motala AA, Kaleebu P, Sandhu MS; African Partnership for Chronic Disease Research (APCDR). Association of HIV and ART with cardiometabolic traits in sub-Saharan Africa: a systematic review and meta-analysis. *Int J Epidemiol*. 2013 Dec;42(6):1754-71. doi: 10.1093/ije/dyt198. Erratum in: *Int J Epidemiol*. 2016 Dec 1;45(6):2210-2211. PMID: 24415610; PMCID: PMC3887568.

²⁸ Davis K, Perez-Guzman P, Hoyer A, Brinks R, Gregg E, Althoff KN, Justice AC, Reiss P, Gregson S, Smit M. Association between HIV infection and hypertension: a global systematic review and meta-analysis of cross-sectional studies. *BMC Med*. 2021 May 13;19(1):105. doi: 10.1186/s12916-021-01978-7. Erratum in: *BMC Med*. 2021 Sep 8;19(1):228. PMID: 33980222; PMCID: PMC8117497.

²⁹ Dzudie A, Hoover D, Kim HY, Ajeh R, Adedimeji A, Shi Q, Pefura Yone W, Nsame Nforiwe D, Thompson Njie K, Pascal Kengne A, Ebasone PV, Barche B, Bissek Anne Cecile ZK, Nash D, Yotebieng M, Anastos K. Hypertension among people living with HIV/AIDS in Cameroon: A cross-sectional analysis from Central Africa International Epidemiology Databases to Evaluate AIDS. *PLoS One*. 2021 Jul 22;16(7):e0253742. doi: 10.1371/journal.pone.0253742. PMID: 34292956; PMCID: PMC8297808.

³⁰ Egede LE, Walker RJ, Monroe P, Williams JS, Campbell JA, Dawson AZ. HIV and cardiovascular disease in sub-Saharan Africa: Demographic and Health Survey data for 4 countries. *BMC Public Health*. 2021 Jun 12;21(1):1122. doi: 10.1186/s12889-021-11218-5. PMID: 34118912; PMCID: PMC8196536.

³¹ Guaraldi G, Prakash M, Moecklinghoff C, Stellbrink HJ. Morbidity in older HIV-infected patients: impact of long-term antiretroviral use. *AIDS Rev*. 2014 Apr-Jun;16(2):75-89. PMID: 24759453.

³² Egger M, Ekouevi DK, Williams C, et al. Cohort Profile: the international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa. *Int J Epidemiol*. 2012;41(5):1256-1264. doi:10.1093/ije/dyr080.

³³ Connelly PJ, Currie G, Delles C. Sex Differences in the Prevalence, Outcomes and Management of Hypertension. *Curr Hypertens Rep*. 2022 Jun;24(6):185-192. doi: 10.1007/s11906-022-01183-8. Epub 2022 Mar 7. PMID: 35254589; PMCID: PMC9239955.

-
- ³⁴ Kautzky-Willer A, Leutner M, Harreiter J. Sex differences in type 2 diabetes. *Diabetologia*. 2023 Jun;66(6):986-1002. doi: 10.1007/s00125-023-05891-x. Epub 2023 Mar 10. Erratum in: *Diabetologia*. 2023 Apr 12;: PMID: 36897358; PMCID: PMC10163139.
- ³⁵ Hema A, Poda A, Tougouma JB, Meda C, Kabore F, Zoungrana J, Kamoule E, Sore I, Bado G, Ouedraogo AS, Sawadogo AB, Millogo A. Sur-risque de diabète sucré et d'hypertension artérielle chez les personnes infectées par le VIH suivies à l'hôpital de jour du CHU Souro Sanou, Bobo-Dioulasso, Burkina Faso, 2018 [Diabetes mellitus and high blood pressure over risk in HIV-infected people followed at Souro Sanou University Hospital Day Hospital, Bobo-Dioulasso 2018]. *Rev Epidemiol Sante Publique*. 2021 Apr;69(2):72-77.
- ³⁶ Peer N, Nguyen KA, Hill J, Sumner AE, Cikomola JC, Nachega JB, Kengne AP. Prevalence and influences of diabetes and prediabetes among adults living with HIV in Africa: a systematic review and meta-analysis. *J Int AIDS Soc*. 2023 Mar;26(3):e26059.