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HIV infection and arterial stiffness among older-adults taking antiretroviral therapy in rural Uganda

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Abstract

HIV infection is associated with arterial stiffness, but no studies have assessed this relationship in sub-Saharan Africa. We enrolled 205 participants over 40 years old in Uganda: 105 on antiretroviral therapy for a median of 7 years, and a random sample of 100 age and gender-matched HIV-uninfected controls from the clinic catchment area. The prevalence of arterial stiffness (ABI>1.2) was 33%, 18%, 19% and 2% in HIV+ men, HIV- men, HIV+ women, and HIV- women. In multivariable models adjusted for cardiovascular risk factors, HIV+ individuals had over double the prevalence of arterial stiffness (APR 2.86, 95%CI 1.41–5.79, *P*=0.003).

Keywords

HIV/AIDS; Uganda; aging; anti-retroviral therapy; arterial stiffness

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Conflicts of Interest

All authors report no conflicts of interest.

Author Roles:

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Introduction

The expansion of HIV therapy to over nine million HIV-infected persons in sub-Saharan Africa has reduced morbidity and mortality from AIDS in the region [1], and is motivating increased attention be paid on the long-term consequences of HIV [2, 3]. In high-income countries, HIV infection is associated with increased prevalence of arterial stiffness [4–6], an important predictor of decreased quality of life, cardiovascular complications and mortality [7–10]. Although some preliminary data suggest that HIV infection might predispose to cardiovascular disease risk in sub-Saharan Africa [11–14], little is known about relationships between HIV infection and arterial stiffness in the region, where differences in genetics, higher rates of parasitic and other co-infections, and altered diet, smoking and physical activity are likely to impact the priority disease states. In this study, we assessed whether HIV infection is associated with arterial stiffness among people on stable ART in rural Uganda.

Methods

Data for this analysis comes from the Ugandan Non-communicable Diseases and Aging Cohort (UGANDAC) Study, NCT02445079), an ongoing cohort study of older-aged people living with HIV in southwestern Uganda [15], and an age and gender-matched, population-based control group of HIV-uninfected individuals enrolled from the clinic catchment area. HIV-infected participants were drawn from the UARTO cohort study, which has been described previously [16, 17], and eligible if they were >40 years of age and had a minimum of 3 years of ART use. HIV-uninfected participants were recruited from Nyakabare Parish, located approximately 20 kilometers from the clinic. Adults in the parish are part of a longitudinal community health survey. All parish residents are eligible for inclusion. We have achieved a >99% response rate, effectively making the study a whole-population survey. We randomly selected adults from the parish who were age and gender-matched to HIV-infected participants. After recruitment and informed consent procedures, an HIV test was performed to confirm their seronegative status.

Participants complete a questionnaire to assess smoking history, and undergo anthropomorphic measurements and blood collection for CD4 count, viral load, lipid profile, and hemoglobin A1c testing (Bayer A1c Now+). Our primary outcome of interest was an ankle brachial index (ABI) ≥1.2, a surrogate of systemic, calcification-related arterial stiffness, which has been correlated with increased risk of all-cause and cardiovascular mortality [7, 18]. A research assistant who completed a two-week training in cardiovascular diagnostics collected all ABI measurements using Doppler-detected (Summit Doppler) systolic blood pressure of the brachial, dorsalis pedis, and posterior tibialis arteries bilaterally. We calculated ABI by dividing the highest of the four ankle pressures by the highest of the two brachial pressures [19].

We estimated the prevalence of arterial stiffness by gender and HIV serostatus, using a Z-test of proportions. We fit generalized linear models with a log link, specifying high ABI as the dependent variable, and adjusting for age, gender, body mass index (BMI), cumulative years of smoking, non-HDL cholesterol [20, 21], and hemoglobin A1c. We fit additional

models restricted to (a) participants less than 60 years old, to assess for evidence of early arteriosclerosis; and (b) only HIV-infected participants to estimate associations between arterial stiffness and HIV-specific factors (CD4 count and a current detectable viral load). Lastly, we included a gender-by-HIV interaction term to assess for differentials relationships between HIV infection and arterial stiffness between men and women. Statistical analyses were conducted with Stata Version 14. Study procedures were reviewed and approved by ethics review committees of Mbarara University of Science and Technology and Partners Healthcare. All participants gave written informed consent.

Results

Approximately half of participants (105/205, 51%) were HIV-infected, with a median ART duration of 7 years (IQR 6.4–7.5), a median nadir CD4 count of 122 (IQR 80-175), and 85/105 (81%) with an undetectable HIV RNA viral load (Supplemental Table 1). Both groups were 50% female and median age was 49 years (IQR 46–53). Participants in the HIV-uninfected control group were more likely to be current or former smokers (50% versus 36%, *P*=0.06), but had a similar median non-HDL cholesterol (107 vs 113 mg/dL, *P*=0.74) and median hemoglobin A1c (5.3 vs. 5.6%, *P*=0.86).

The prevalence of vascular stiffness was 33% (17/51) among HIV-infected men, 18% (9/50) among HIV-uninfected men, 19% (10/54) in HIV-infected women, and 2% (1/50) in HIV-uninfected women (Figure S1). In multivariable models adjusted for cardiovascular risk factors, HIV infection was associated with an increased prevalence of arterial stiffness (adjusted prevalence ratio [APR] 2.86, 95%CI 1.41–5.79, *P*=0.003, Table 1). This association was particularly pronounced among those less than 60 years old (APR 4.05, 95%CI 1.74–9.52, *P*=0.001). We found no associations between nadir CD4, current CD4, or detectable viral load and arterial stiffness. The prevalence ratio of arterial stiffness by HIV-infection was 9.26 in women (19 vs 2%) and 1.85 in men (33 vs 18%), although the interaction term was not statistically significant (APR 5.00, *P*=0.14).

Discussion

HIV-infection is associated with a more than doubling in the prevalence of arterial stiffness in Uganda. Although we were not powered to discern a difference in association by gender, we found evidence of arterial stiffness in only 2% of HIV-uninfected women compared with nearly 20% of HIV-infected women. These associations have important implications for HIV programs in sub-Saharan Africa, home to over 25 million people with HIV infection, because arterial stiffness is strongly predictive of both cardiovascular events and all-cause mortality [9, 10].

The pathophysiology of arterial stiffness in HIV infection is putatively caused by a combination of HIV-mediated endothelial dysfunction and viral infection of arterial smooth muscle [22, 23]. The causative role of HIV replication is also supported by prior studies, which, in contrast to ours, detected increasing risk of arterial stiffness with decreasing nadir CD4 count [5, 24]. The lack of association seen in our study could be explained by the fact that over 80% of our study population had a CD4 nadir less than 200. Alternatively, regional

differences in genetics, diet, and locally relevant co-infections might also alter relationships between HIV-infection and cardiovascular disease risk. Our study also provides preliminary evidence of gender patterning in this setting. This finding requires confirmation, as prior studies in western populations comparing HIV-infected and uninfected groups have included few women [4] or have not assessed for an interaction effect by gender [5, 25].

If our findings are corroborated, an important next step will be to identify modifiable behaviors or interventions for prevention and mitigation of HIV-associated arterial stiffness. Early initiation of ART might be preventive given prior associations between nadir CD4 and arterial stiffness. Therapeutic options might also exist if ABI measurements were incorporated into routine HIV care. For example, avoidance of protease inhibitors could reduce risk [26], and HMG-CoA reductase inhibitors have shown promise in HIV infected populations [27, 28].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary

HIV infection is associated with arterial stiffness, but no studies have assessed this relationship in sub-Saharan Africa. We enrolled 205 participants over 40 years old in Uganda: 105 on antiretroviral therapy for a median of 7 years, and a random sample of 100 age and gender-matched HIV-uninfected controls from the clinic catchment area. The prevalence of arterial stiffness (ABI>1.2) was 33%, 18%, 19% and 2% in HIV+ men, HIV- men, HIV+ women, and HIV- women. In multivariable models adjusted for cardiovascular risk factors, HIV+ individuals had over double the prevalence of arterial stiffness (APR 2.86, 95%CI 1.41–5.79, P=0.003).

Table 1

Generalized linear models estimating the relative prevalence of high ABI (>1.2) by known correlates of arterial stiffness.

Characteristic	Prevalence Ratio (95%CI)	P-value	Adjusted Prevalence Ratio (95%CI)	P-value
Age (each 10 years)	1.03 (0.71–1.48)	0.88	1.38 (0.95–2.01)	0.09
Female gender	0.41 (0.21–0.79)	0.007	0.49 (0.24–1.02)	0.06
BMI				
<18	1.05 (0.41–2.68)	0.91	0.96 (0.37–2.50)	0.94
18–25	REF	--	REF	--
25–30	0.57 (0.21–1.53)	0.26	0.47 (0.14–1.62)	0.23
>30	0.63 (0.16–2.39)	0.49	1.25 (0.29–5.34)	0.76
Cumulative years of smoking (each 10 years)	1.06 (0.86–1.30)	0.58	0.95 (0.75–1.21)	0.69
Non-high density lipoprotein cholesterol (each mg/dL)	0.99 (0.98–1.00)	0.02	0.99 (0.98–1.00)	0.07
Hemoglobin A1c (each 1% A1c)	1.01 (0.73–1.39)	0.94	1.11 (0.86–1.43)	0.44
HIV Infection	**2.57 (1.31–5.03)**	**0.006**	**2.86 (1.41–5.79)**	**0.003**