

Electrocardiographic Evidence of Cardiac Disease by Sex and HIV Serostatus in Mbarara, Uganda



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Numerous studies in the United States and Europe have demonstrated an increased risk for cardiovascular disease (CVD) among persons living with human immunodeficiency virus (PLWH) [1]. The relationship between human immunodeficiency virus (HIV) and subsequent CVD has not been as well established in sub-Saharan Africa (SSA). PLWH in SSA have a high burden of untreated risk factors, but results vary regarding surrogate markers of CVD. Data on outcomes, such as stroke or myocardial infarction, are limited.

An analysis of data from the SMART (Strategies for Management of Antiretroviral Therapy) trial found that PLWH had a high prevalence of electrocardiography (ECG) abnormalities at baseline, which predicted CVD risk over the study period [2]. We investigated the prevalence of ECG abnormalities by HIV serostatus in rural Uganda to estimate differences in CVD risk. As secondary aims, we assessed: 1) ECG evidence of ischemic coronary artery disease by HIV serostatus; and 2) sex-based differences in ECG findings.

We collected cardiovascular disease risk factors and 12-lead ECGs on PLWH taking ART for a minimum of three years, as well as age- and sex-matched, community-dwelling, HIV-negative controls. We fit log binomial regression models to estimate the association between HIV serostatus and ECG abnormalities, both in the entire cohort and stratified by sex. A significant proportion of study participants had major ECG abnormalities (55, 18%) and/or evidence of underlying ischemia (29, 9%), but no statistically significant differences by HIV serostatus were observed. Women were significantly more likely than men to have ECG evidence of ischemia (adjusted prevalence ratio [APR] 2.71, $p = 0.01$), independent of HIV serostatus. Although HIV infection is associated with an increased risk of cardiac disease in high income countries, we did not find an increased proportion of ECG abnormalities among PLWH on long-term ART in Uganda. Additional research is warranted to investigate the sex-based differences we detected in this population.

METHODS

Data were obtained from the UGANDAC (Ugandan Non-communicable Diseases and Aging Cohort) study, a

prospective study of PLWH ($n = 155$) and age- and sex-matched HIV-negative comparators ($n = 154$) living within the HIV clinic catchment area [3]. Participants were eligible for enrollment if they were >40 years of age and, for PLWH, taking antiretroviral therapy for >3 years.

Participants completed demographic questionnaires and underwent anthropomorphic measurement, blood pressure measurement, and blood collection for lipid profile, hemoglobin A1c, and inflammatory markers. HIV viral load and CD4+ T cell counts were extracted from clinical records.

A resting 12-lead ECG was collected using a Nasiff CardioCard digital ECG machine (Central Square, New York, USA). ECGs were interpreted by board-certified cardiologists (A.A. and B.K.) according to American Heart Association standard criteria [4]. We selected 2 primary outcomes: 1) presence of ≥ 1 major ECG abnormality; and 2) evidence of myocardial ischemia. An ECG was defined as abnormal if it included left or right bundle branch block, intraventricular conduction delay, atrial fibrillation, left atrial abnormality, left or right axis deviation, left or right ventricular hypertrophy, diagnostic Q waves, ST-segment depression, or abnormal QTc interval. We selected this composite score because each abnormality has been associated with an additive risk of cardiovascular mortality in prior cohort studies [5]. An ECG was categorized as ischemic if it included >1 -mm horizontal or down-sloping ST-segment depressions, T-wave inversion >2 mm in a vascular territory, or diagnostic Q waves in a vascular territory [4].

We estimated the proportion of individuals with ≥ 1 ECG abnormality and with ischemic changes on ECG. We fit binomial log regression models with both HIV serostatus and sex as primary predictors of interest. Predictors of cardiac risk, including age, systolic blood pressure, low-density cholesterol, body mass index, and socioeconomic status, were included in the final multivariable model if statistically significant on univariate analysis ($p < 0.25$). All procedures were approved by the Mbarara University of Science and Technology Research Ethics Committee, the Ugandan National Council of Science and Technology, and Partners HealthCare Research Committee.

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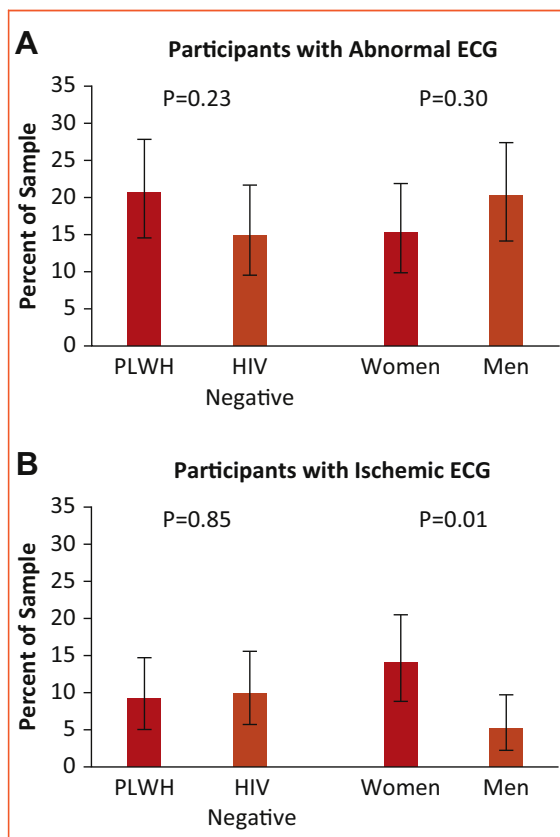


FIGURE 1. Electrocardiography (ECG) differences by sex and serostatus, percent and 95% confidence interval. A: Proportion of study individuals with an abnormal ECG. B: Proportion of study individuals with an ischemic ECG. HIV, human immunodeficiency virus; PLWH, persons living with human immunodeficiency virus.

RESULTS

A total of 309 individuals were enrolled with a mean age of 51 years. Half (50.2%) were PLWH (Online Table 1). Compared with PLWH, HIV-negative persons had a higher prevalence of current smoking (20.8% vs. 5.8%; $p < 0.01$), underweight (17.5% vs. 8.4%; $p = 0.06$), and bottom-tertile asset ownership (48.1% vs. 26.1%; $p < 0.01$). PLWH had a higher mean C-reactive protein ($p < 0.01$). Most PLWH (83%) had an undetectable viral load at the time data was collected and were taking a non-nucleoside reverse transcriptase inhibitor-based regimen (91.6%).

Women were more likely than men to have diabetes (9.9% vs. 1.9%; $p = 0.03$) and to be overweight (42.4% vs. 10.1%; $p < 0.01$). Women also had higher low-density lipoprotein ($p < 0.01$) and C-reactive protein levels ($p < 0.01$) but were less likely to smoke (3.3% vs. 22.8%; $p < 0.01$).

The most common ECG abnormalities were left atrial abnormality ($n = 20$, 6.5%), left ventricular hypertrophy ($n = 14$, 4.5%), and interventricular conduction delay

($n = 11$, 3.6%) (Online Table 2). Ischemic abnormalities were seen in 9.4% ($n = 29$) of the total cohort. There was no significant difference in the prevalence of ≥ 1 ECG abnormality (20.7 vs. 14.9%; $p = 0.23$) or ischemic change (9.0% vs. 9.7%; $p = 0.85$) by HIV serostatus (Figure 1). These findings persisted after multivariable adjustment in log binomial regression models. However, there was a significantly higher prevalence of ischemic ECGs among women compared with men in both univariable (prevalence ratio: 2.75; 95% confidence interval: 1.26 to 6.01; $p = 0.01$) and multivariable adjusted models (prevalence ratio: 2.71; 95% confidence interval: 1.23 to 5.94; $p = 0.01$) (Online Table 3).

DISCUSSION

We found no statistically significant differences in the prevalence of abnormal or ischemic ECGs among middle-aged, ambulatory PLWH on antiretroviral therapy compared with HIV-negative individuals in rural Uganda. In contrast, we did detect a significantly higher prevalence of ischemic ECGs among women compared with men, irrespective of HIV serostatus.

Data on the relationship between HIV and CVD in SSA are mixed. In Ghana, HIV infection has not been shown to increase the risk of carotid atherosclerosis [6], but in Uganda, previous studies demonstrate an increased prevalence of carotid atherosclerosis and peripheral arterial disease associated with HIV-related systemic inflammatory markers [7]. In Malawi, HIV infection has been identified as the single most important risk factor for ischemic stroke among individuals < 45 years of age and contributes strongly to the burden of stroke in older individuals [8].

One possible explanation for our findings is that the mechanisms underlying CVD risk differ for PLWH. Magnetic resonance imaging and autopsy studies in Malawi suggest that PLWH are at risk for a nonatherosclerotic vasculopathy [8]. Similarly, a South African study found PLWH with acute coronary syndromes were more likely to have single-vessel acute thrombus than multivessel atherosclerosis, possibly related to endothelial activation in the setting of chronic inflammation [9]. ECG may therefore underestimate the risk of CVD outcomes among PLWH.

Multiple studies from SSA have also demonstrated a higher prevalence of cardiac risk factors in women, including hypertension, obesity and angina [10]. These differences may represent an increased burden of cardiac disease among women in the region. Our study demonstrated significantly higher rates of obesity, diabetes, and cholesterol levels among women, in addition to higher rates of ischemic change on ECG. Such findings suggest a region-specific approach is necessary to avoid underdiagnosis of CVD among women in SSA.

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