HHS Public Access

Author manuscript

Glob Heart. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

Glob Heart. 2019 December ; 14(4): 395–397. doi:10.1016/j.gheart.2019.08.007.

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

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INTRODUCTION

Numerous studies in the United States and Europe have demonstrated an increased risk for cardiovascular disease (CVD) among persons living with HIV (PLWH).[1] The relationship between 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.

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Conflict of Interest and Financial Disclosure Statement

The authors report no relationships that could be construed as a conflict of interest. This work was supported by the U.S. National Institutes of Health (R21 HL124712, P30 AI060354, R24 AG044325, P30 AG024409, R01 MH113494), the MGH Executive Committee on Research, and Friends of a Healthy Uganda. The authors acknowledge the following additional sources of support; K23 MH099916; K43 TW010715; K01 TW01021 and R01 MH118107

An analysis of data from the SMART trial found that PLWH had a high prevalence of 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 a) ECG evidence of ischemic coronary artery disease by HIV serostatus and b) sex-based differences in ECG findings.

METHODS

Data were obtained from the Ugandan Non-communicable Diseases and Aging Cohort (UGANDAC), a prospective study of PLWH (n=155) and age and sex-matched HIV-negative comparators (n=154) living within the clinic catchment area.[3] Participants were eligible for enrollment if they were >40 years old and, for PLWH, taking ART 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. ECGs were interpreted by board-certified cardiologists (AA and BK) according to American Heart Association standard criteria.[4] We selected two 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 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: >1mm horizontal or down-sloping ST-T segment depressions, T wave inversion >2mm 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, BMI 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.

RESULTS

309 individuals were enrolled with a mean age of 51. Half (50.2%) were PLWH (Supplemental Table 1). Compared to 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 CRP

(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 LDL (p<0.01) and CRP 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 inter-ventricular conduction delay (n=11, 3.6%, Supplemental 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 [PR] 2.75, 95%CI 1.26–6.01, p=0.01) and multivariable adjusted models (APR 2.71, 95%CI 1.23–5.94, p=0.01, Supplemental Table 3).

DISCUSSION

We found no statistically significant differences in the prevalence of abnormal or ischemic ECGs among middle-aged, ambulatory PLWH on ART 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 aged <45 years 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. MRI and autopsy studies in Malawi suggest that PLWH are at risk for a non-atherosclerotic vasculopathy.[8] Similarly, a South African study found PLWH with acute coronary syndromes were more likely to have single-vessel acute thrombus than multi-vessel 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 under-diagnosis of CVD among women in SSA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors wish to thank the staff and participants of the UARTO and UGANDAC studies for their important contributions to this work.

List of Abbreviations

CVD	Cardiovascular Disease
PLWH	Persons Living with HIV
SSA	Sub-Saharan Africa
ECG	Electrocardiogram
BMI	Body Mass Index
CRP	C-reactive Protein
sCD14	soluble CD14
sCD163	soluble CD163
PR	Prevalence ratio
APR	Adjusted prevalence ratio

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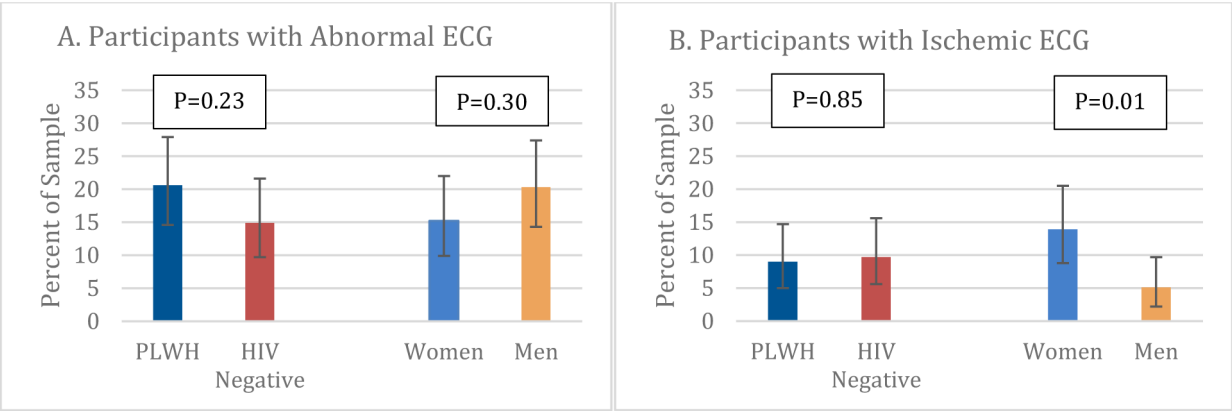

Figure 1:
ECG Differences by Sex and Serostatus, Percent and 95% Confidence Interval