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Predicting cardiovascular risk using a novel risk score in young and middle-age adults with HIV: associations with biomarkers and carotid atherosclerotic plaque

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Abstract

Background: Traditional risk factors associated with cardiovascular disease (CVD) include older age, smoking, poor diet, lack of exercise, obesity, high blood pressure, high cholesterol, and family history. Young-to-middle age adults (YMAA) are less often identified as being at risk of CVD, but traditional risk scores primarily target older adults and do not accurately estimate risk among YMAA.

Methods: This study examined biomarkers associated with CVD risk in YMAA in the context of HIV and cocaine use; risk was assessed by two methods: (1) a relative cardiovascular (CV) risk score that includes several factors and (2) carotid atherosclerotic plaque. Associations between

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CVD risk (CV risk score and carotid atherosclerotic plaque) and proinflammatory cytokines, markers of immune activation, HIV status, and cocaine use were examined. Participants (N = 506) included people with and without HIV and people who use or do not use cocaine.

Results: Participants' mean age was 36 (SD = 9.53); half (51%) were men. Cocaine use and C-reactive protein were associated with greater relative CV risk scores, but no associations between biomarkers and CV risk emerged. Age and CV risk scores were associated with carotid atherosclerotic plaque, but biomarkers were not. HIV was not associated with CV risk scores or carotid atherosclerotic plaque.

Conclusions: Among YMAA, CV risk scores may help providers identify lifestyle changes needed among those at risk for CVD before more advanced risk (e.g., atherosclerotic plaque) is identified. Implications are discussed.

Keywords

HIV; cocaine use; cardiovascular risk

Introduction

Among people with human immunodeficiency virus (HIV) on antiretroviral therapy (ART), cardiovascular disease (CVD) is the leading cause of mortality.[1] The increased risk of CVD in people with HIV (PWH) is associated with risk factors that include chronic comorbid conditions (hypertension, diabetes, dyslipidemia, chronic kidney disease, and smoking),[2-5] side effects of ART (accelerated atherosclerosis),[5-8] and HIV-related inflammation and immune activation.[9,10] The increased immune system activation associated with HIV may contribute to both CVD and other chronic health problems.[11,12]

Risk of CVD among PWH is also associated with substance use; cocaine users are at greater risk of cardiovascular complications.[13,14] Excessive cocaine use is associated with both acute and chronic cardiovascular toxicity,[15-17] myocardial ischemia,[18] myocardial infarction,[19] arrhythmias,[20] and cardiomyopathy.[21-23] Additionally, PWH who use cocaine have an increased risk of type 2 myocardial infarctions, which can be attributed to oxygen demand and supply mismatch associated with cocaine use.[24]

Because HIV and cocaine use are independent risk factors for cardiovascular complications, the combination of the two may exacerbate risk for CVD. PWH using cocaine have greater proportions of coronary calcification, lesions, calcified area/volumes and calcium scores,[25] coronary artery calcification, and ART-associated coronary atherosclerosis.[26] Cocaine use, CVD, and HIV are independently associated with increased inflammation.[9,10,27,28] However, traditional CVD screening risk factors target older age, smoking, poor diet, lack of exercise, obesity, high blood pressure, high cholesterol, and family history. As such, young-to-middle age adults (YMAA) with HIV who use cocaine would be less likely to be identified as at risk of CVD.

Atherosclerotic plaque is associated with CVD, and carotid intima-media thickness measured via ultrasound has broadly demonstrated efficacy in identification of plaque.[29,30] In addition, HIV and cocaine users experience high levels of psychological stress.[31,32]

Psychological stress is not accounted for in existing risk calculators for CVD. However, these and several factors can affect the development of plaque and CVD risk, and according to accumulation of risk theories, risks can accumulate over the life course to increase the risk for CVD.[33] A superior method of evaluating relative CVD risk may include the use of composite scores incorporating behavioral and psychological variables such as age, sex, heredity, smoking, blood pressure, body mass index (BMI), stress levels, pre-existing CVD, physical activity, and diet that account for the accumulation of risk for CVD.[34]

Biomarkers are critical to the study of CVD prevention and quantification of risk. A few biomarkers, such as C-reactive protein (CRP), are significant CVD risk predictors. Other biomarkers associated with CVD include increased cytokines, markers of immune cell activation, and vascular growth factors such as interleukin-6 (IL-6),[35] tumor necrosis factor (TNF-α),[35,36] soluble CD14 and CD163, and vascular endothelial growth factor (VEGF).[37,38] Less-studied biomarkers associated with myocardial death and injury are pentraxin 3 and endothelin-1.[35,39,40]

Traditional risk scores, such as the Framingham risk score, or the American Heart Association risk score traditionally requires that a person be at least 40 years old for the calculation of a risk score. However, novel risk scores, such as the one proposed by Zdrenghea et al.[34], do not rely on age for the calculation of risk. Therefore, this study examined biomarkers associated with CVD risk in YMAA in the context of HIV and cocaine use, in which risk was assessed by two methods: (1) a relative cardiovascular (CV) risk score that included smoking, age, sex, BMI, HIV, and cocaine use and (2) carotid atherosclerotic plaque.[34] Associations were examined between CVD risk (CV risk score and carotid atherosclerotic plaque) and proinflammatory cytokines, markers of immune activation, HIV status, and cocaine use. It was hypothesized that relative CV risk assessment among (YMAA) in this sample would be comparable to risk identified by carotid atherosclerotic plaque and that both assessments would be associated with biomarkers of immune activation

Method

Participants

Approval for this study was obtained from the University of Miami Miller School of Medicine Institutional Review Board. Written informed consent was obtained from participants prior to any study-related activities. The study was conducted in South Florida, USA; enrollment began in December 2014 and ended in June 2018. Eligible participants were 18–50 years old and not actively on ART at the time of study enrollment. Screening included assessment of cocaine use and HIV status; exclusion criteria included pre-identified CVD risk, history of diabetes mellitus, hyperlipidemia, hypertension, receiving statins, vascular events (e.g., myocardial infarctions, stroke, transient ischemic attacks, angioplasty, or bypass surgery), or hepatitis C; other criteria have been previously described.[38]

Study Design

This was a cross-sectional descriptive study.

Measures

Outcomes

Carotid artery plaque.: Carotid artery plaque was assessed using a high-resolution B-mode carotid ultrasound system by a certified vascular technologist blinded to the participants' HIV and cocaine use status. Carotid ultrasound was performed according to standard scanning and reading protocols as detailed previously.[41] Ultrasonographic readings (n = 400) were taken from the left and the right carotid arteries at 1-cm segment of the distal common carotid artery near and far wall, 1 cm of bifurcation, and 1-cm proximal internal carotid artery near and far wall. Plaque was defined as an area of focal wall thickening 50% greater than surrounding wall thickness and measured by an automated edge tracking system, M'Ath.[42] M'Ath uses an intensity gradient detection algorithm to determine both the presence and number of plaque sites.

CV risk score calculator.: In order to compute an overall measure of CV disease risk, a modified version of a relative risk formula proposed by Zdrenghea et al.[34] was used. This risk score, compared to other risk scores of CVD, is not limited to older adults and can be used among YMAA. A relative CV score was calculated using demographic characteristics, as well as family history, smoking, blood pressure, BMI, and psychosocial stress, and previous history of CVD (MI, stroke, TIA, angioplasty, or bypass surgery) and hypertension diagnosis were also included in the CV risk calculation. Similarly, protective factors, such as eating habits and exercise, were taken into consideration. Further detail on these individual risk factors included in risk calculation is described below:

Demographic and lifestyle characteristics.: Demographic information collected at baseline included age and sex. If participants were men younger than 40 or women younger than 40, risk increased by 1 point, and 2 points for men between the ages of 40 to 65 or women between the ages of 50 to 75, risk increased by 2 points. For men older than 65 or women older than 75, risk increased by 3 points. Participants were also asked to report on smoking; if any smoking was reported, 2 points were added to the risk score; 1 point otherwise.

Heredity.: Participants were asked to report on parental family history of CVD dichotomously (yes/no). Risk increased by 1 point for participants with a family history without CVD younger than 60 years of age; 2 points were added for participants with parental history of CVD younger than 60 years of age.

History of CVD.: Participants were asked to report on their history of CVD dichotomously (yes/no). If participants reported a history of CVD, 10 points were added to their risk score; if participants did not report a history of CVD, zero points were added.

Physical assessment.: During a physical assessment, participants' weight and height was measured and used to calculate BMI. A BMI less than 30 added 1 point of risk; a BMI of 30 or greater added 2 points in risk. Systolic and diastolic blood pressure were assessed using the average of three measurements. Participants with systolic or diastolic blood pressure values of <140/90 mmHg had 1 point added to their risk score; participants above this had

2 points added. If participants had ever been prescribed medication for high blood pressure, they were given 2 points regardless of blood pressure value.

Psychosocial stress.: Psychosocial stress was measured using one item from the Center for Epidemiological Studies-Depression Scale (CES-D).[43] Respondents provided the frequency of depressive symptoms in the past week on a scale from 0 (*Rarely*) to 3 (*Most or all of the time*). For the present study, however, only one item was used, "I was bothered by things that usually don't bother me." In this sample, internal consistency for the full CES-D was excellent ($\alpha = 0.92$). Participants endorsing feeling stressed most or all of the time were given 2 points.

Physical activity.: Physical activity and exercise was assessed using The International Physical Activity Questionnaire,[44,45] a measure that examines minutes and days of the past week in which individuals walk, perform moderate activity, perform vigorous activity, and remain sitting. These values are multiplied together in order to calculate the average number of minutes spent weekly in these domains. If participants reported at least 150 min of exercise per week, the overall score was reduced by 25%.

Eating habits.: Using items from the Rapid Eating Assessment for Participants (REAP),[46] if participants reported frequently having 2–3 servings of fruits and vegetables per day, or never/rarely choosing higher fat red meats like prime rib, T-bone steak, hamburger, ribs, etc., instead of lean red meats, the overall risk score was reduced by 15%, consistent with recommendations.[34]

Predictors

HIV status.: HIV testing was performed using the rapid test OraQuickADVANCE® Rapid HIV-1/2 Antibody Test among those who self-reported being HIV-uninfected. HIV-infected participants provided documentation to confirm their HIV status. The clinician conducting HIV testing and assessment was a trained HIV counselor and provided pre- and post-test counseling to participants.

Cocaine use.: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth Edition (DSM-IV), non-patient version (SCID-IV-NP) was used to assess cocaine use and was administered by a trained professional under the supervision of a licensed clinical psychologist.[47] The SCID has high reliability.[48]

Physical assessment.: During a physical assessment, waist circumference was measured.[49]

Immune activation markers: Soluble SCD14 and SC163.: Plasma levels of sCD14 and sCD163 were determined by ELISA using the Human Quantikine Immunoassay (R&D Systems) following the manufacturer's instructions. For sCD14 measurement, samples were diluted 400-fold, and results are expressed in pg/mL. For sCD163 measurement, samples were diluted 30-fold, and results are expressed in pg/mL.

Inflammatory cytokines and growth factors.: IL-1α, IL-6, TNF-α, and VEGF plasma levels were computed using a tailored MILLIPLEX Human Cytokine Magnetic Bead

Panel (EMD Millipore, Billerica, MA) in accordance with the manufacturer's instructions. Immediately preceding measurement, plasma samples were thawed, vortexed, and centrifuged at 1000× for 3 min. Samples were incubated overnight using a mixture of beads for IL-1α, IL-6, TNF-α, and VEGF at 4°C with shaking. Subsequent washing was followed by incubation with biotinylated detection Abs for 1 h at room temperature. After streptavidin-PE was added to the wells, an additional incubation period of 30 min concurred at room temperature. Beads were subsequently washed and diluted with 150 μL sheath fluid prior to procurement using a MAG-PIX instrument (Luminex Corporation). Mean fluorescence intensity (MFI) data were assessed via MILLIPLEX Analyst Software V.3.5 (EMD Millipore). Mean cytokine concentrations were resolved using standard curve and represented in pg/ml.

C-reactive protein.: Overnight fasting blood samples were obtained by venous puncture, and after serum was separated from red blood cells, it was frozen at −80°C until analyzed. The high-sensitive C-reactive protein (hs-CRP) was measured by immunoassays using the enzyme-linked immunosorbent assay (ELISA) kits (Enzo Life Sciences, Inc, Farmingdale, NY), with sensitivity of 10.810 ng/mL (0.001081 mg/dL).

Monocytes, lymphocytes CD309+CD34$^+$, and CD309+CD133$^+$.: Lymphocytes, monocytes, and EPCs were identified by flow cytometry after staining of whole blood using fluorochrome-conjugated antibodies specific to CD45, CD34, CD309, and CD133. Briefly, 200 μL whole blood was stained with antibodies for 20 min at room temperature followed by lysis of RBC using RBC lysis buffer. The cells were then washed and fixed at 4°C. Fixed cells were acquired on a BD FACSCalibur and analyzed using Flow Jo software. Total lymphocytes were identified based on the side scatter properties and CD45$^+$ expression. Monocytes were identified based on the forward and side scatter properties to exclude the majority of lymphocytes, NK cells, and granulocytes. From the monocyte gate, EPCs were identified as frequencies of monocytes expressing CD309+CD34$^+$ cells, and immature progenitor cells (IPC) were identified as frequencies of monocytes expressing CD309+CD133+. Both EPC and IPC were expressed as frequencies of monocytes.

Lipopolysaccharide.: Lipopolysaccharide (LPS) levels were measured in the serum sample by the use of the Limulus amebocyte lysate chromogenic endpoint assay (19059, Stem cell Technologies) according to the manufacturer's recommendations. Samples were diluted at a ratio of 1:5 in endotoxin-free water and heat-inactivated at 80°C for 10 min prior to the assay. LPS concentration in the samples was calculated in relation to an E. coli endotoxin standard and expressed in pg/mL.

Analytic plan—Descriptive statistics (means, medians, standard deviations, and proportions) were examined and used to describe the sociodemographic characteristics of participants. To determine differences in CV risk scores between HIV status and cocaine groups, a two-way analysis of variance (-ANOVA) was conducted with cocaine and HIV status as predictors; an interaction of cocaine and HIV status was included. Then, a series of multiple regressions were fit to predict plaque as an outcome using maximum-likelihood estimation with various link functions (identity and logit) and distributions (Gaussian and

binomial) as well as robust standard errors. For CV risk scores, an ordinary regression using a Gaussian distribution with an identity link was used. For binary responses, a logistic regression with a logit link with a binomial distribution was used. Biomarkers were standardized by z-score transformation, subtracting the sample mean and then dividing by the sample standard deviation. Missing data, which included left-censored values, were imputed using multiple imputation. To ensure this method of imputation was appropriate, missing data analyses were performed to determine associations with missingness. All presented coefficients were unstandardized. Statistical analyses were conducted using SPSS version 24.

Results

Sociodemographic characteristics

Characteristics of baseline participants (N = 506; HIV− COC− n = 200, HIV+ COC− n = 100, HIV+ COC+ n = 106, HIV− COC+ n = 100) included an average age of 36.18 years (SD = 9.53). Table 1 shows all baseline demographics as well as all variables by group. Table 2 shows bivariate correlations among all biomarkers.

Missing and non-detectable data

There was no missing data in demographic characteristics, cocaine use, HIV status, waist circumference, and total BMI. However, plaque (1% missingness due to difficulties measuring participants' plaque) and biomarkers had a wide range of missing or non-detectable data due to technical difficulties or values being low or non-detectable. Missing and non-detectable values did not differ by group (ps > 0.494). Participant sex, ethnicity, and age were examined in association with missing and non-detectable values. Only missing or non-detectable IL-6 values were related to participant sex (p = 0.002) and age (p = 0.036). Both age and sex were subsequently controlled for in analyses including Il-6.

CV risk by HIV and cocaine use

CV risk was analyzed with a 2 (HIV status: HIV negative versus HIV positive) 2 (Cocaine Use: No use versus Use) between-subjects ANOVA. The main effect of HIV status bordered on significance, $F(1,501) = 3.87$, $p = 0.05$. The main effect of cocaine use on CV risk was significant, $F(1, 501) = 28.63$, $p < 0.001$. There was a non-significant interaction between HIV status and cocaine use, $F(1,501) = 0.24$, $p = 0.626$. Cocaine users had a CV risk average of 6.89 (SE = 0.1), whereas non-users had an average CV risk of 6.21 (SE = 0.09).

HIV status, cocaine use, and biomarkers predicting CV risk

A generalized linear model with an identity link and Gaussian family was fit to analyze potential associations between HIV status, cocaine use, and biomarkers with CV risk. Examining the pooled coefficients, only cocaine use ($B = -0.64$, $p = 0.002$) and CRP ($B = 0.23$, $p = 0.001$) were associated with CV risk. The full model is presented in Table 3.

Smoking, Sex, Age, Waist Circumference, HIV Status, Cocaine Use, and Biomarkers Predicting Carotid Atherosclerotic Plaque

The generalized linear model with a logit link and binomial family (logistic regression) of smoking, sex, age, waist circumference, HIV status, cocaine use, and biomarkers predicting plaque was performed. However, as detailed in Table 4, only age was found to be a significant predictor of plaque (odds ratio (OR) = 1.17 [95% confidence interval (CI) 1.13, 1.21]). Specifically, on average a 1-year increase in age was associated with a 17% increase in the odds of having carotid atherosclerotic plaque detected.

HIV status, cocaine use, and CV risk predicting carotid atherosclerotic plaque

A generalized linear model with a logit link and binomial family (logistic regression) was fit to analyze potential associations between HIV status, cocaine use, and CV risk predicting carotid plaque. The pooled coefficient for CV risk was found to be a significant predictor of carotid atherosclerotic plaque (OR = 1.34 [95% CI 1.16, 1.56]). A summary of this model is presented in Table 5.

Discussion

This study evaluated the relationship between proinflammatory cytokines, markers of immune activation (such as CRP), HIV status, cocaine use and cardiovascular risk scores, and carotid atherosclerotic plaque among YMAA and found higher CV risk to be associated with cocaine use and CRP. However, cocaine use did not interact with HIV to increase their combined impact on CV risk scores. A one-point increase in CV relative risk score was associated with approximately 34% increase in odds of having carotid atherosclerotic plaque, after controlling for HIV status, cocaine use, and the interaction between HIV status and cocaine use. In contrast, among traditional predictors of CVD, that is, smoking, sex, age, waist circumference, and risk factors, that is, HIV status, cocaine use, and biomarkers, only age predicted carotid atherosclerotic plaque.

CRP was associated with higher CV risk scores, in line with previous studies.[50-52] Some research suggests that not only is CRP a surrogate marker for CVD, but it is also directly involved in CVD causality through increased production of IL-6 in a dose-dependent relationship.[53] In addition to being strongly promoted by IL-6, CRP may also be a weak stimulant of further IL-6 production by monocytes.[54] Previous research has found additional biomarkers (e.g., IL-6, soluble CD-40, TNF-α, natriuretic peptides, and IL-18) to be associated with CV risk.[55,56] Cytokines and markers of immune activation, including higher levels of sCD14 (ng/mL) and soluble sCD163, have been associated with HIV among virally suppressed PWH on treatment.[57] However, proinflammatory cytokines and markers of immune activation were not associated with CV risk scores or carotid atherosclerotic plaques in this study. It is likely that IL-6 (pg/mL) was not associated with CVD in our study because research demonstrates that short-term IL-6 activation (which is likely in our young patient population) is protective toward heart tissue.[58,59] Conversely, long-term IL-6 activation, specifically amongst patients over the age of 65, has been associated with pathogenic damage to the cardiovascular system and CVD, although causality cannot be established.[60,61] A systematic review on this topic found that of the 10 studies investigating

the influence of inflammatory cytokines (IL-6, IL-8, IL-10, IL-17, and TNF-α), only half demonstrated a statistically significant association with CVD.[62] Ultimately, analyzing individual associations between proinflammatory cytokines and CVD can make finding statistically significant results challenging.

Contrary to expectation, HIV status was not associated with increased CV risk scores or carotid atherosclerotic plaque, perhaps due to the younger age of the study population or the unexpectedly high prevalence of carotid atherosclerotic plaque across all groups (19% to 33%); in previous research, rates of 18% have been reported.[63] These higher rates across groups may have been related to the higher percentage of Black people in this sample, given that Black people are at greater risk for cardiovascular disease.[64]

Traditional CVD risk factors include older age, lack of physical activity, obesity, hypertension, smoking, diabetes, high cholesterol, and an echocardiogram demonstrating left ventricular hypertrophy.[65] However, even if individuals maintain a healthy weight and lifestyle, age ultimately becomes a risk factor for cardiovascular disease,[66] as found in this study and reported in prior research.[67] These results may suggest that the incremental CV risk incurred by HIV infection may not emerge in young adulthood, and as such not cause carotid atherosclerotic plaques. Further research into other predictive markers of CVD in PWH remains needed. The development of a CV risk scoring system for younger individuals, specifically those with HIV, can play an important role in helping providers identify patients in need of lifestyle changes to reduce the risk for CVD before more advanced forms of risk (e.g., atherosclerotic plaque) are identified. Considering the high rates of psychological stress among those who use substances as well as those with HIV,[31,32] an advantage of the CV score was its estimation of risk accounting for psychological stress. Several effective easily accessible behavioral and psychological interventions, including web- and computer-based interventions, exist for managing stress[68] and could prove to be effective in preventing CVD.[69]

Cocaine use was associated with CV risk, but this risk did not interact with HIV to increase CV risk scores or predict carotid atherosclerotic plaque. Although both cocaine and HIV have known associations with cardiovascular pathology, the combined effect of cocaine and HIV on the myocardium has not been extensively studied. Analyses of gross specimens postmortem reaffirmed previous findings that chronic cocaine use results in concentric hypertrophy of the left ventricle of the heart, which contributed to diastolic dysfunction and heart failure.[70] However, when Mosunjac et al.[70] observed the effects of HIV and cocaine use together, there was no interactive effect of cocaine use and HIV. Other studies have similarly found no synergistic association between HIV and cocaine use as risk factors for CVD. The commonality among all of these studies is the age of participants. The mean age for participants investigated in these studies ranged from 28 to 36 years, which is likely too young to demonstrate overt signs of CVD.[70,71] It is also likely that because CVD markers have primarily been studied among older adults, the sensitivity of tools to determine risk is not sufficiently high to detect risk in young populations. Although our study did not find a combined association between HIV and cocaine as risk factors for the presence of plaque, it did reaffirm the results of previous studies indicating cocaine contributes to increase CV risk above and beyond other known risk factors.[15,23,72] Because this study was conducted

among YMAA, plaque may not have developed yet; however, they appear to remain at risk for future CVD.

Limitations and strengths

Some limitations must be considered in interpreting the results of this study. First, though biomarkers may be reliable and reproducible, they can be difficult to collect, and values may be excluded if they are outside reference limits or are within discrimination limits.[56] Thus, associations with other biomarkers in this study may have been obscured due to inherent limitations in collection. In addition, this study was cross-sectional in nature, limiting causal interpretation, and some of the risk factors considered in composite CV risk scores were measured using single items (e.g., stress), as opposed to more comprehensive, validated measures. Last, carotid atherosclerotic plaque was analyzed using the presence of plaque as opposed to other characteristics of plaques such as size and morphology that can be measured using ultrasound.[73] These limitations should be addressed in future research.

Despite these limitations, this study also had several strengths. First, this study makes an important contribution to the investigation of several biomarkers in association with CVD risk, as measured by the presence of plaque in the carotid artery and a composite CV risk score for people across the lifespan. The use of a composite score for people across the lifespan is an advantage over other widely used methods of calculating risk, which may underestimate risk in YMAA or provide misleadingly low risk estimates for younger individuals. Second, the biomarkers in this study have rarely been assessed simultaneously in the context of HIV and cocaine use. As such, our findings emphasized the importance of CRP above other biomarkers in this population, consistent with previous research in the general population.[74] Third, this study examined asymptomatic YMAA with multiple risk factors, in whom plaque may not have been expected to have developed or in whom providers would not expect to have plaques. In this process, we identified that the presence of plaque in the carotid artery in this sample was highly prevalent (25%) and even more so among HIV-seropositive cocaine users (33%).

Conclusion

In summary, this study explored associations between proinflammatory cytokines, markers of immune activation, cardiovascular risk scores, and carotid atherosclerotic plaque in the context of HIV and cocaine use. Although associations failed to emerge between HIV and CV risk scores and carotid atherosclerotic plaques in this sample of YMAA, the frequency of arterial plaque highlights the need for CVD risk assessment tools that can be used in clinical practice. Associations between CV risk markers and cocaine suggest that cocaine use is related to subclinical cardiac injury, which may be linked to later cardiac events. The use of CV risk scores for YMAA may help providers identify the need for lifestyle changes among patients at risk for CVD before more advanced forms of risk (e.g., atherosclerotic plaque) are identified.

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Table 1.

Baseline demographics and dependent variables by group (N = 506).

	All	HIV−/COC−	HIV+/COC−	HIV+/COC+	HIV−/COC+
	M (SD)	*M* (SD)	*M* (SD)	*M* (SD)	*M* (SD)
	N (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Variable	***N* = 506**	***n* = 200**	***n* = 100**	***n* = 106**	***n* = 100**
Age	36.18 (9.53)	34.34 (8.98)	34.60 (10.69)	40.82 (8.66)	36.54 (8.64)
Sex					
Male	256 (50.7)	102 (51.0)	35 (35.0)	45 (43.5)	74 (74.0)
Female	250 (49.4)	98 (49.0)	65 (65.0)	61 (57.5)	26 (36.0)
Ethnicity					
Caucasian	57 (11.3)	22 (11.0)	5 (5.0)	12 (11.3)	18 (18.0)
African American	313 (61.9)	116 (58.0)	73 (73.0)	76 (71.7)	48 (48.0)
Haitian	13 (2.6)	7 (3.5)	5 (5.0)	1 (0.9)	0 (0.0)
Hispanic/Latino Caucasian	96 (19.0)	41 (20.5)	13 (13.0)	15 (14.2)	27 (27.0)
Hispanic/Latino Black	12 (2.4)	5 (2.5)	2 (2.0)	2 (1.9)	3 (3.0)
Other	15 (3.0)	9 (4.5)	2 (2.0)	0 (0.0)	4 (4.0)
Income (monthly)					
US$0–US$500	215 (42.7)	75 (37.5)	34 (34.0)	47 (44.3)	59 (60.2)
US$500–US$1000	194 (38.5)	57 (28.5)	54 (54.0)	52 (49.1)	31 (31.6)
US$1000–US$5000	89 (17.7)	64 (32.0)	12 (12.0)	7 (6.6)	6 (6.1)
US$5000–US$10000	4 (0.8)	2 (1.0)	0 (0.0)	0 (0.00)	2 (2.0)
US$10000+	2 (0.4)	2 (1.0)	0 (0.0)	0 (0.00)	0 (0.0)
Outcomes Plaque					
No	373 (74.6)	153 (78.1)	81 (81.0)	70 (66.7)	69 (69.7)
Yes	127 (25.4)	43 (21.9)	19 (19.0)	35 (33.3)	30 (30.3)
CV Risk	6.45 (1.43)	6.05 (1.30)	6.36 (1.42)	6.99 (1.44)	6.79 (1.46)
Predictors					
Waist circumference	95.40 (16.39)	96.17 (17.35)	96.16 (17.73)	91.75 (16.15)	96.98 (12.51)
sCD14 (ng/mL)	1786.11 (521.00)	1677.77 (381.01)	1973.07 (412.48)	1994.57 (675.13)	1629.68 (499.51)
sCD163 (ng/mL)	611.53 (363.77)	525.15 (269.14)	747.89 (417.52)	729.62 (412.54)	543.37 (360.89)

Variable	All *M* (SD) *N* (%) *N* = 506	HIV−/COC− *M* (SD) *n* (%) *n* = 200	HIV+/COC− *M* (SD) *n* (%) *n* = 100	HIV+/COC+ *M* (SD) *n* (%) *n* = 106	HIV−/COC+ *M* (SD) *n* (%) *n* = 100
IL-1α (pg/mL)	68.55 (76.56)	67.33 (72.17)	61.80 (58.68)	73.62 (102.98)	72.67 (65.93)
IL-6 (pg/mL)	7.73 (15.82)	6.40 (7.30)	9.14 (25.55)	7.21 (8.99)	9.07 (14.96)
TNF-α (pg/mL)	18.70 (22.49)	10.60 (9.10)	30.44 (35.83)	33.24 (22.54)	10.12 (8.51)
VEGF (pg/mL)	79.23 (96.45)	62.84 (67.82)	106.28 (108.14)	96.00 (137.22)	70.34 (79.78)
LPS (pg/mL)	154.05 (51.48)	141.42 (38.26)	167.68 (59.06)	191.62 (60.05)	130.90 (31.20)
CRP (mg/L)	1964.41 (787.53)	1965.85 (771.84)	2170.10 (749.33)	1988.66 (802.54)	1739.70 (793.82)
$CD309^{+}CD34^{+}$ (% of MG)	0.40 (0.90)	0.33 (0.75)	0.33 (0.36)	0.66 (1.69)	0.42 (0.63)
$CD309^{+}CD133^{+}$ (% of MG)	11.12 (193.57)	3.26 (35.90)	1.15 (4.54)	0.92 (1.24)	41.94 (405.76)
Lymphocytes (%)	27.92 (9.76)	28.47 (8.96)	30.26 (10.52)	26.28 (9.27)	25.78 (10.28)
Monocytes (%)	5.61 (2.15)	5.43 (1.83)	5.79 (2.32)	5.83 (2.42)	5.63 (2.34)

MG: monocyte gate; CV: cardiovascular; IL-6: interleukin-6; TNF-α: tumor necrosis factor; VEGF: vascular endothelial growth factor; LPS: lipopolysaccharide; CRP: C-reactive protein.

Note. Group combinations presented as (HIV status/cocaine status).

Table 2.

Correlations among biomarkers.

	IL-1α (pg/mL)	IL-6 (pg/mL)	TNF-α (pg/mL)	VEGF (pg/mL)	LPS (pg/mL)	sCD14 (ng/mL)	sCD163 (ng/mL)	CRP (mg/L)	$CD309^+CD34^+$	$CD309^+CD133^+$	Lymphocytes (%)	Monocytes (%)
IL-1α (pg/mL)	—											
IL-6 (pg/mL)	0.199 *	—										
TNF-α (pg/mL)	−0.02	0.580 **	—									
VEGF (pg/mL)	−0.048	0.05	0.250 **	—								
LPS (pg/mL)	−0.023	0.163 *	0.319 **	0 094 *	—							
sCD14 (ng/mL)	0.001	−0.04	0.246 **	0.089 *	0.201 **	—						
sCD163 (ng/mL)	−0.036	−0.057	0.286 **	0.109 *	0.248 **	0.323 **	—					
CRP (mg/L)	−0.033	0.039	0.144 **	0.159 **	0.272 **	0.159 **	0.184 **	—				
$CD309^+CD34^+$	0.106	0.006	0.091	−0.009	0.092	0.166 **	0.042	−0.013	—			
$CD309^+CD133^+$	−0.002	0.059	0.054	0.098 *	0.120 *	0.171 **	−0.006	0.04	0.620 **	—		
Lymphocytes (%)	0.038	0.001	−0.025	−0.034	0.016	−0.027	−0.113 *	−0.029	−0.069	−0.049	—	
Monocytes (%)	−0.005	−0.02	0.055	0.037	−0.023	0.139 **	0.044	−0.008	−0.129 **	−0.057	0.152 **	—

CV: cardiovascular; IL-6: interleukin-6; TNF-α: tumor necrosis factor; VEGF: vascular endothelial growth factor; LPS: lipopolysaccharide; CRP: C-reactive protein.

Note.

*Correlation is significant at the 0.05 level (2-tailed).

**Correlation is significant at the 0.01 level (2-tailed).

Table 3.

Multivariable models HIV status, cocaine use, and biomarkers predicting CV risk ($N = 506$).

Variable	*B*	SE	95% CI	*p*	FDR-corrected *p*
(Intercept)	5.14	0.30	4.55, 5.74	<0.001	0.008
HIV status (ref = HIV positive)	0.23	0.21	−0.19, 0.65	0.280	0.435
Cocaine use (ref = non-cocaine user)	−0.39	0.20	−0.78, 0	0.049	0.157
HIV status cocaine use	−0.37	0.25	−0.86, 0.11	0.131	0.363
Gender (ref = women)	−0.34	0.12	−0.57, −0.1	0.005	0.020
Age	0.05	0.01	0.04, 0.06	0.000	<0.001
IL-1α (pg/mL)[a]	−0.05	0.10	−0.24, 0.14	0.607	0.694
IL-6 (pg/mL)[a]	−0.13	0.13	−0.38, 0.12	0.299	0.434
TNFα (pg/mL)[a]	0.03	0.10	−0.16, 0.22	0.749	0.799
VEGF (pg/mL)[a]	0.09	0.05	−0.01, 0.2	0.077	0.185
LPS (pg/mL)[a]	0.05	0.07	−0.09, 0.19	0.515	0.634
sCD163 (ng/mL)[a]	0.07	0.06	−0.05, 0.2	0.261	0.435
sCD14 (ng/mL)[a]	−0.12	0.07	−0.26, 0.02	0.081	0.185
CRP (mg/L)[a]	0.20	0.06	0.07, 0.32	0.002	0.011
$CD309^{+}CD34$ (%)$^{+}$[a]	0.06	0.09	−0.11, 0.23	0.460	0.613
$CD309^{+}CD133$ (%)$^{+}$[a]	−0.02	0.10	−0.21, 0.18	0.877	0.877

FDR: false discovery rate correction for multiple comparisons; SE: standard error; CI: confidence interval; IL-6: interleukin-6; TNF-α: tumor necrosis factor; VEGF: vascular endothelial growth factor; LPS: Lipopolysaccharide; CRP: C-reactive protein.

[a]Standardized using a z-score transformation.

Table 4.

Smoking, gender, age, waist circumference, HIV status, cocaine use, and biomarkers predicting plaque (N = 506).

Variable	*B*	SE	OR	95% CI	*p*	FDR-corrected *p*
(Intercept)	−8.02	1.25			<0.001	<0.001
Smoking (ref = yes)	−0.3	0.28	0.74	−0.84, 0.24	0.281	0.743
Gender (ref = women)	0.08	0.26	1.08	−0.42, 0.58	0.756	0.881
Age	0.16	0.02	1.17	0.12, 0.19	<0.001	<0.001
Waist circumference	0.01	0.01	1.01	−0.01, 0.03	0.391	0.784
HIV status (ref = HIV positive)	0.14	0.46	1.15	−0.76, 1.03	0.761	0.881
Cocaine use (ref = cocaine user)	−0.14	0.45	0.87	−1.01, 0.74	0.761	0.881
HIV status x cocaine use	0.13	0.56	1.13	−0.96, 1.22	0.820	0.881
IL-1α (pg/mL)[a]	0.23	0.24	1.25	−0.26, 0.72	0.357	0.784
IL-6 (pg/mL)[a]	−0.24	0.29	0.79	−0.82, 0.35	0.424	0.784
TNF-α (pg/mL)[a]	−0.15	0.23	0.86	−0.61, 0.31	0.518	0.871
VEGF (pg/mL)[a]	−0.02	0.12	0.98	−0.25, 0.21	0.893	0.918
LPS (pg/mL)[a]	−0.06	0.17	0.94	−0.39, 0.27	0.727	0.881
sCD163 (ng/mL)[a]	−0.15	0.15	0.86	−0.44, 0.15	0.326	0.784
sCD14 (ng/mL)[a]	−0.04	0.15	0.96	−0.33, 0.25	0.801	0.881
CRP (mg/L)[a]	−0.03	0.15	0.97	−0.32, 0.26	0.833	0.881
$CD309^{+}CD34$ (%)$^{+}$[a]	0.19	0.16	1.21	−0.12, 0.5	0.220	0.663
$CD309^{+}CD133$ (%)$^{+}$[a]	0.05	0.17	1.05	−0.29, 0.38	0.781	0.881

FDR: false discovery rate correction for multiple comparisons; SE: standard error; OR: odds ratio; CI: confidence interval; IL-6: interleukin-6; TNF-α: tumor necrosis factor; VEGF: vascular endothelial growth factor; LPS: Lipopolysaccharide; CRP: C-reactive protein.

[a]Standardized using a z-score transformation.

Table 5.

HIV status, cocaine use, and CV risk predicting plaque ($N = 506$).

Variable	*B*	SE	OR	95% CI	*p*	FDR-corrected *p*
(Intercept)	−2.79	0.6			<0.001	<0.001
HIV status (ref = HIV positive)	−0.09	0.31	0.91	−0.7, 0.52	0.775	0.881
Cocaine use (ref = cocaine user)	−0.6	0.34	0.55	−1.27, 0.08	0.082	0.337
HIV status cocaine use	0.36	0.44	1.44	−0.5, 1.23	0.407	0.784
CV risk	0.3	0.08	1.34	0.15, 0.44	<0.001	<0.001

FDR: false discovery rate correction for multiple comparisons; OR: odds ratio; CI: confidence interval; CV: cardiovascular.

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