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MAJOR ARTICLE

Visceral Adiposity Index as a Measure of Cardiovascular Disease in Persons With Human Immunodeficiency Virus

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Background. Persons with well-treated human immunodeficiency virus (HIV) demonstrate a 2-fold higher risk of cardiovascular disease (CVD), which may be related to excess visceral adipose tissue (VAT). The visceral adiposity index (VAI) is a score to approximate VAT by combining biochemical measures with anthropometrics without quantification by imaging. We evaluated VAI in association with cardiometabolic factors among persons with HIV (PWH).

Methods. Forty-five PWH on antiretroviral therapy and virologically controlled with increased abdominal VAT (VAT area >110 cm^2 on CT) and no known CVD were included. VAI was calculated using standard sex-specific formulas. Coronary plaque was assessed using coronary CT angiography.

Results. Participants were predominantly male (73%), white (53%), and non-Hispanic (84%), with a mean age of 55 (standard deviation, 7) years. Among PWH, median VAI was calculated to be 4.9 (interquartile range [IQR], 2.8–7.3). Log VAI correlated with log VAT ($r = 0.59$, $P < .0001$) and anthropometric measures (body mass index: $r = 0.36$, $P = .02$; waist circumference: $r = 0.43$, $P = .004$; waist-to-hip ratio: $r = 0.33$, $P = .03$). Participants with coronary plaque had a higher VAI compared to those without coronary plaque (median, 5.3 [IQR, 3.4–10.5] vs 2.8 [IQR, 1.8–5.0]; $P = .004$). VAI (area under the curve = 0.760, $P = .008$) performed better than the atherosclerotic CVD risk score to predict the presence of plaque in receiver operating characteristic analyses.

Conclusions. VAI may be a useful biomarker of metabolic dysfunction and increased CVD risk that may occur with VAT accumulation in PWH.

Clinical Trials Registration. NCT02740179.

Keywords. cardiovascular disease; coronary plaque; HIV; visceral adipose tissue; visceral adiposity index.

Persons with human immunodeficiency virus (PWH) develop a redistribution of body fat, demonstrating a relatively greater accumulation of visceral adipose tissue (VAT) when compared to persons without human immunodeficiency virus (HIV) for similar body mass index (BMI). Visceral fat is more inflamed and promotes dysmetabolism, which could have important implications for the pathogenesis of cardiovascular disease (CVD) [1]. Metabolic sequelae of VAT accumulation include insulin resistance, dyslipidemia, endothelial dysfunction, and atherosclerosis [2, 3], which are all leading drivers of CVD and prevalent risk factors in the HIV population.

With the advent of effective antiretroviral therapy (ART), PWH can achieve good virological control, but ART alone does not mitigate the risk of CVD in HIV—a risk that is estimated to be almost double that of persons without HIV [4]. We have previously shown that increased VAT among well-treated PWH is associated with both radiologic findings (presence of plaque and coronary artery calcification) [3] and circulating biomarkers (lipoprotein-associated phospholipase A2, oxidized low-density lipoprotein [LDL], high-sensitivity cardiac troponin T) [5] that are predictive of CVD. In this way, excess VAT may account for the disproportionate CVD risk in PWH.

Computed tomography (CT) or magnetic resonance imaging (MRI) are the current gold-standard imaging modalities for quantification of VAT [6]. These modalities are impractical for everyday use and are limited by cost, safety, and availability in the outpatient clinical setting.

Received 23 May 2023; accepted 18 July 2023; published online 24 July 2023

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https://doi.org/10.1093/ofid/ofad398

The visceral adiposity index (VAI) was introduced by Amato et al as a sex-specific formula using anthropometric and biochemical data in the general population from western Sicily [7]. Evaluation of the VAI in other populations has been useful to identify those at increased risk for metabolic disease [8]. The VAI may be a valuable score incorporated into routine clinical care to help stratify metabolic risk in HIV. There are limited data investigating VAI in HIV, and in the current study, we evaluated VAI in association with cardiometabolic factors among PWH.

METHODS

Study Participants

Data evaluated in this cross-sectional study were leveraged from a randomized controlled trial (RCT) performed at Massachusetts General Hospital and Brigham and Women's Hospital that aimed to evaluate a therapeutic strategy to improve subclinical myocardial disease in HIV [9]. Forty-five PWH who received a baseline coronary CT angiography were included in this separate analysis, unique from the aims of the RCT. Participants were 40–65 years of age, on continuous ART >12 months, demonstrated HIV viral suppression (HIV RNA <100 copies/mL), and had increased visceral adiposity on abdominal CT (VAT ≥110 cm^2). Participants were excluded for known history of CVD, cerebrovascular disease, uncontrolled diabetes (hemoglobin A1c ≥7.5% and/or insulin use), uncontrolled blood pressure (>140/90 mm Hg), liver disease (alanine aminotransferase [ALT] >3 times the upper limit of normal), and kidney disease (creatinine >1.5 mg/dL or estimated glomerular filtration rate <60 mL/minute/1.73 m^2). Participants on chronic statin therapy were permitted to enroll, but those with <1 year of use were excluded. Pregnant women or those actively trying to conceive were excluded.

Patient Consent Statement

All participants provided written informed consent to participate. This study was reviewed and approved by the Mass General Brigham Human Research Committee (Boston, Massachusetts).

Anthropometry

Anthropometric measures were obtained by licensed dieticians at the Massachusetts General Hospital Translational and Clinical Research Center. BMI (kg/m^2) was assessed using standard weight and height measurements. Waist circumference (WC [cm]) was taken using anatomic reference points of the top of the iliac crest. Waist-to-hip ratio (WHR) was calculated by taking the iliac WC and dividing by hip circumference, measured at the broadest part of the hip. Laboratory parameters, including triglycerides (TG [mg/dL]) and high-density lipoprotein (HDL [mg/dL]) were obtained following an overnight fast. VAI was calculated using the published sex-specific formulas [7]:

$$\text{Females:}\quad \text{VAI} = \frac{\text{WC}}{36.58 + (1.89 \times \text{BMI})} \times \frac{\text{TG}}{0.81} \times \frac{1.52}{\text{HDL}}$$

$$\text{Males:}\quad \text{VAI} = \frac{\text{WC}}{39.68 + (1.88 \times \text{BMI})} \times \frac{\text{TG}}{1.03} \times \frac{1.31}{\text{HDL}}$$

Body Composition Phenotyping

Abdominal VAT and subcutaneous adipose tissue (SAT) areas were quantified at the level of the L4 pedicle on a single-slice noncontrast CT scan. Scan parameters were standardized for individual images (144 table height, 80 kV, 70 mA, 2 seconds, 10-mm slice thickness, 48 cm field of view). Fat was defined as voxels with an attenuation from −50 to −250 Hounsfield units (HU). Using commercial software (Vitrak, Merge e/Film), an offline analysis utilizing tracings was performed to evaluate abdominal VAT and SAT areas [3].

HIV-Specific Parameters

Ultrasensitive reverse-transcription polymerase chain reaction (Roche COBAS Amplicor) was utilized to determine the HIV viral load with a lower limit of detection of 20 copies/mL. CD4 cell counts were assessed by flow cytometry.

Atherosclerotic Cardiovascular Disease Risk Score

The atherosclerotic cardiovascular disease (ASCVD) risk score was calculated using the pooled cohort equation encompassing age, sex, race, total cholesterol, HDL, systolic blood pressure, and history of hypertension, diabetes mellitus, and tobacco use.

Atherosclerotic Plaque Characteristics by Cardiac CT Angiography

The cardiac CT protocol included a noncontrast electocardiogram (ECG)–synchronized CT to quantify coronary artery calcium (CAC) score, followed by a contrast-enhanced ECG-synchronized coronary CT angiogram to assess any coronary plaque (calcified, noncalcified, mixed), stenosis, and vulnerable plaque features. A 128- and 192-slice dual-source CT scanner (Definition Flash and Force, Siemens Healthineers, Erlangen, Germany) was used with a standardized protocol that included assessment of calcified and noncalcified plaque segments consistent with the Society of Cardiovascular Computed Tomography guidelines [10, 11]. We assessed the presence of vulnerable plaque features, defined based on any 1 of 3 features: positive remodeling (remodeling index >1.1), low CT attenuation (<30 HU), and napkin-ring sign (low central attenuation with ring-like peripheral high attenuation). All analyses were performed on a dedicated workstation (Aquarius Intuition, TeraRecon).

Statistical Analysis

Data are reported as mean (standard deviation [SD]) for normally distributed variables and median (interquartile range [IQR]) for

nonnormally distributed variables. Categorical variables were reported as percentages. Nonnormally distributed variables were log transformed for further analyses. Linear regression was performed by Pearson correlation coefficient using normally distributed variables and log-transformed nonnormally distributed variables. Between-group comparisons were assessed by the Student's *t* test using normalized data. Receiver operating characteristic (ROC) curves were generated for measures of body composition (VAI, VAT, BMI, WC, WHR) and ASCVD risk score. The optimal cutoff values of sensitivity and specificity were determined to understand predictors of CAC >0 and presence of plaque. Statistical significance was considered for a P value of <.05. Analyses were performed using JMP version 16.

RESULTS

Clinical Characteristics

PWH were predominantly of male sex (73%), White race (53%), and non-Hispanic ethnicity (84%), with a mean age of 55 (SD, 7) years. With regard to HIV-specific parameters, there was a long duration of HIV and ART use (mean, 20 [SD, 8] years and 12 [SD, 4] years, respectively). The majority of participants had achieved viral suppression and demonstrated good immunologic control with a median CD4 count of 754 (IQR, 608–950) cells/μL. Most PWH were on nucleoside reverse transcriptase inhibitor and integrase inhibitor–containing regimens, while only 11% were currently on protease inhibitor–containing regimens. Few PWH had current aspirin (11%) and current statin use (18%), while 20% reported current tobacco use. Lipid profiles were generally well controlled (median LDL, 110 [IQR, 90–129] mg/dL; median TG, 142 [IQR, 88–203] mg/dL). ASCVD risk scores were low to borderline risk (median, 6.0 [IQR, 2.4–10.0]) (Table 1).

Table 1. Baseline Characteristics (N = 45)

Characteristic	
Demographics	
Age, y, mean (SD)	55 (7)
Race, No. (%)	
White	24 (53)
Black	13 (29)
>1 race	2 (5)
Other	6 (13)
Hispanic ethnicity, No. (%)	7 (16)
Male sex, No. (%)	33 (73)
HIV parameters	
$CD4^+$ count, cells/μL, median (IQR)	754 (608–950)
Log_{10} HIV RNA viral load, copies/mL, mean (SD)	1.36 (0.19)
Duration of HIV, y, mean (SD)	20 (8)
Duration of ART use, y, mean (SD)	12 (4)
Current PI use, No. (%)	5 (11)
Current NRTI use, No. (%)	45 (100)
Current NNRTI use, No. (%)	18 (40)
Current integrase inhibitor use, No. (%)	29 (66)
Body composition and ectopic fat	
BMI, kg/m^2, mean (SD)	31.9 (5.8)
Iliac waist circumference, cm, mean (SD)	109.4 (13.2)
WHR, mean (SD)	0.98 (0.07)
VAT area, cm^2, median (IQR)	189 (127–267)
SAT area, cm^2, median (IQR)	337 (219–429)
VAT:SAT, median (IQR)	0.68 (0.40–0.88)
VAI, median (IQR)	4.9 (2.8–7.3)
Metabolic parameters	
Current aspirin use, No. (%)	5 (11)
Current statin use, No. (%)	8 (18)
SBP, mm Hg, mean (SD)	129 (10)
DBP, mm Hg, median (IQR)	78 (72–83)
Current tobacco use, No. (%)	9 (20)
Current alcohol use, No. (%)	18 (40)
Creatinine, mg/dL, mean (SD)	0.96 (0.15)
HbA1c, %, median (IQR)	5.5 (5.3–6.0)
ALT, U/dL, median (IQR)	24 (17–30)
Total cholesterol, mg/dL, median (IQR)	184 (169–206)
Triglycerides, mg/dL, median (IQR)	142 (88–203)
HDL cholesterol, mg/dL, median (IQR)	46 (43–54)
LDL cholesterol, mg/dL, median (IQR)	110 (90–129)
ASCVD risk score, %, median (IQR)	6.0 (3.4–10.0)

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IQR, interquartile range; LDL, low-density lipoprotein, NNRTI, nonnucleoside reverse transcriptase inhibitor, NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SAT, subcutaneous adipose tissue; SBP, systolic blood pressure, SD, standard deviation; VAI, visceral adiposity index; VAT, visceral adipose tissue, WC, waist circumference; WHR, waist-to-hip ratio.

Body Composition

More than half of the PWH were in the obese category (mean BMI, 31.9 [SD, 5.8] kg/m^2). PWH had increased WC (mean, 109.4 [SD, 13.2] cm). Median VAT area measured by abdominal CT scan was 189 (IQR, 127–267) cm^2. Median VAI was calculated to be 4.9 (IQR, 2.8–7.3) (Table 1).

Relationships of VAI With Metabolic Parameters

Among other measures of body composition, log VAI correlated with log VAT ($r = 0.59$, $P < .0001$), log VAT:SAT ratio ($r = 0.37$, $P = .01$), and WHR ($r = 0.33$, $P = .03$). Log VAI did not correlate with SAT. In addition, log VAI correlated with log ALT ($r = 0.32$, $P = .03$). As expected, WC, TG, and HDL, which are incorporated into the VAI calculation, correlated with log VAI (Supplementary Table 1).

Relationships of VAI With Plaque Parameters

VAI was higher among PWH with detectable CAC (CAC score >0) compared to those without any CAC (CAC = 0) (median, 4.9 [IQR, 3.4–11.2] vs 3.1 [IQR, 2.0–6.2]; $P = .03$); similarly, VAI was higher among PWH with presence of any coronary plaque compared to those with absence of any plaque (median, 5.3 [IQR, 3.4–10.5] vs 2.8 [IQR, 1.8–5.0]; $P = .004$) (Figure 1). The VAI tended to be higher regardless of type of plaque (calcified vs noncalcified). Evaluating further for plaque

phenotype, VAI was increased among PWH who had any high-risk plaque feature versus those without any high-risk plaque feature (median, 6.1 [IQR, 3.4–11.2] vs 3.5 [IQR, 2.3–5.3]; $P = .047$) (Table 2). Other traditional anthropometrics that can be obtained in the clinical setting, such as BMI, WC, and WHR, were not significantly different when stratifying by either detectable and undetectable CAC or presence and absence of plaque (Supplementary Table 2).

Predictors of Plaque Parameters

VAI was the best predictor of CAC >0 (best cutoff value = 3.35, sensitivity 84%, specificity 52%, area under the curve [AUC] = 0.687, $P = .04$) and presence of any plaque (best cutoff value = 3.35, sensitivity 83%, specificity 63%, AUC = 0.760, $P = .008$) when compared to other measures of body composition (VAT, BMI, WC, WHR). VAI also performed better than ASCVD risk score for predicting CAC >0 and presence of plaque (Tables 3 and 4 and Figure 2*A* and 2*B*).

DISCUSSION

In the current study, we highlight the VAI as a potential marker to screen for visceral adiposity and associated CVD risk among PWH. The VAI was calculated using measures that can be obtained as part of clinical care and correlated well with sophisticated radiographic measures for fat redistribution and atherosclerosis on CT imaging. VAI appears to be the best predictor of the presence of coronary artery disease as compared with other measures of body composition and may perform better than the well-recognized ASCVD risk score. VAI may help identify PWH with subclinical coronary artery disease by leveraging visceral adiposity as a biomarker, which could provide useful information for risk stratification and CVD prevention.

The VAI incorporates a combination of anthropometric and lipid parameters, thus offering an advantage over checking anthropometric measures, such as BMI and WC, alone. Several anthropometric measures have been used to estimate visceral adiposity, including BMI, WC, and WHR, but have shown inconsistent relationships to CVD risk [12, 13]. Moreover, BMI, WC, and WHR are unable to differentiate the visceral from the subcutaneous depot. The addition of the lipid parameters to anthropometrics in the VAI may discern who may be more prone to metabolic dysfunction and home in on an at-risk phenotype. Though WC measures are not typically part of routine care and would require training and additional time to ascertain for calculation of the VAI, the VAI may still provide a more practical alternative to CT imaging to assess CVD risk.

Current gold-standard measures of VAT include cross-sectional imaging by CT [14]. Dual-energy X-ray absorptiometry measures VAT indirectly by calculating the difference between total fat and SAT and has been evaluated as an alternative method, but it generally lacks accuracy in assessing VAT [15]. When evaluating for VAT, imaging procedures are primarily used for research purposes and have cost implications and increase radiation exposure, which limits routine use in clinical practice. The VAI is a feasible option, as it is cost-effective using diagnostics obtained as a part of routine clinical care.

We showed that PWH with CAC scores >0 and presence of any coronary plaque (calcified, noncalcified, or mixed) had higher VAI scores compared to those PWH without evidence of CAC or any coronary plaque. The population we studied were of borderline ASCVD risk and without symptoms. The large Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study recently confirmed that approximately 56% of persons with HIV with borderline ASCVD risk and no known history of CVD,

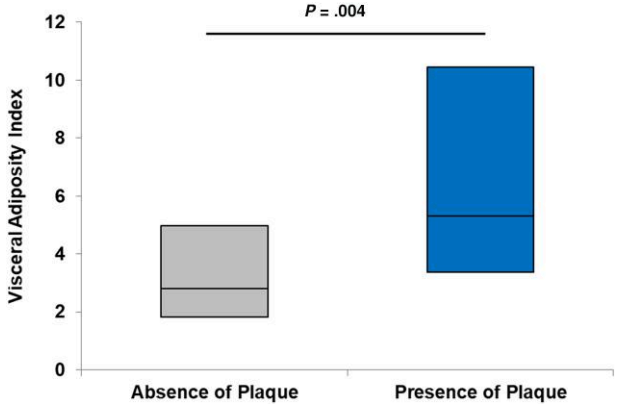

Figure 1. Comparison of visceral adiposity index (VAI) among people with human immunodeficiency virus (PWH) without known cardiovascular disease in the absence or presence of plaque as assessed on coronary computed tomography angiography. Box plot represents the 25th and 75th percentiles and line within the box represents the median. VAI was higher among PWH with presence of any coronary plaque compared to those without any presence of plaque (median, 5.3 [interquartile range {IQR}, 3.4–10.5] vs 2.8 [IQR, 1.8–5.0]; $P = .004$).

Table 2. Comparison of Visceral Adiposity Index by Coronary Computed Tomography Angiography Parameters

Visceral Adiposity Index, Median (IQR)		*P* Value[a]
CAC = 0	CAC >0	
3.1 (2.0–6.2)	4.9 (3.4–11.2)	.03
Absence of plaque	Presence of plaque	
2.8 (1.8–5.0)	5.3 (3.4–10.5)	.004
Absence of calcified plaque	Presence of calcified plaque	
3.4 (2.3–6.7)	5.1 (3.4–8.5)	.07
Absence of noncalcified plaque	Presence of noncalcified plaque	
3.6 (2.3–6.9)	7.1 (4.1–11.2)	.10
Absence of mixed plaque	Presence of mixed plaque	
3.6 (2.3–7.8)	4.9 (3.4–11.2)	.13
Absence of any high-risk plaque	Presence of any high-risk plaque	
3.5 (2.3–5.3)	6.1 (3.4–11.2)	.047

Abbreviations: CAC, coronary artery calcium; IQR, interquartile range.

[a] *P* value given after performing Student's *t* test on log-transformed data.

Table 3. Efficacy of Indices in Predicting Coronary Artery Calcium

Index	Best Cutoff Value	Sensitivity, %	Specificity, %	AUC
VAI	3.35	84	52	0.687[a]
VAT, cm^2	252	47	81	0.589
BMI, kg/m^2	32.6	63	52	0.524
WC, cm	122.4	32	95	0.570
WHR	1.04	42	90	0.614
ASCVD risk score, %	6.30	67	63	0.659

Abbreviations: ASCVD, atherosclerotic cardiovascular disease risk score; AUC, area under the curve; BMI, body mass index; CAC, coronary artery calcium score; VAI, visceral adiposity index; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist-to-hip ratio.

[a]Indicates model is significant ($P < .05$).

Table 4. Efficacy of Indices in Predicting Presence of Coronary Plaque

Index	Best Cutoff Value	Sensitivity, %	Specificity, %	AUC
VAI	3.35	83	63	0.760[a]
VAT, cm^2	212	63	75	0.609
BMI, kg/m^2	26.6	33	94	0.549
WC, cm	113.0	54	69	0.538
WHR	1.01	46	88	0.635
ASCVD risk score, %	8.80	48	86	0.675

Abbreviations: ASCVD, atherosclerotic cardiovascular disease risk score; AUC, area under the curve; BMI, body mass index; VAI, visceral adiposity index; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist-to-hip ratio.

[a]Indicates model is significant ($P < .05$).

who would not otherwise have indication to receive statin treatment, have subclinical atherosclerosis and evidence of plaque despite being presumed to have relatively lower risk [11]. In this way, it would be important to find a marker, such as VAI, that could discern presence of CAC or plaque among those for whom the risk may not be fully understood based on traditional risk factors. Large cohorts have repeatedly shown a link of fat redistribution to atherosclerotic disease in HIV [3, 16, 17]. With regard to body composition, VAT has been shown to be a good predictor of CVD risk in the general population. VAT volume and VAT:SAT as measured on fluorodeoxyglucose–positron emission tomography/CT were associated with increased risk for CVD events, whereas other body composition measures, including BMI and SAT, were not predictive of CVD events [18]. VAT and VAT:SAT ratio, but not SAT, correlated strongly with VAI in our study, suggesting a unique relationship of VAI to the metabolically adverse visceral depot as compared to the subcutaneous depot.

No clinical cutoffs have been established using VAI to predict cardiometabolic disease in any population. Some studies have suggested cutoffs in certain populations based on stratifying VAI into tertiles or quartiles [19–23]. Within the National Health and Nutrition Examination Survey cohort evaluating older participants, a VAI >1.7 was associated with an increased risk of mortality [24]. To place our study of PWH in context, the median VAI was 4.9 in a group selected for increased VAT. Findings taken from the United Kingdom biobank also demonstrated that VAI was associated with an increased risk for both all-cause and CVD-related mortality [25]. A study among those without known CVD demonstrated VAI to be a better indicator of 10-year CVD incidence compared to BMI and WHR [26]. In addition, VAI was shown to be a marker of subclinical atherosclerosis among those at risk for developing diabetes, correlating well with carotid intima-media thickness independent of other CVD risk factors [27].

Compared to other body composition measures, VAI was a better predictor of CAC and any presence of coronary plaque when we evaluated the ROC, while other measures did not distinguish those with versus those without coronary artery disease. Moreover, VAI performed better than the ASCVD risk score. VAI may offer an advantage over VAT or ASCVD risk assessment alone by combining central adiposity along with traditional CVD risk factors, such as lipids and sex. Studies have shown that ASCVD risk score may underestimate risk of CVD in HIV [28], so VAI may provide an alternative marker to assess PWH for CVD risk. Our data were remarkable for a VAI cutoff of 3.35, and larger studies are needed to assess what VAI cutoff should be used to discriminate CVD risk in HIV. While VAI performed better in our models, the AUC was of moderate discriminatory value, and the specificity was low. Therefore, future studies should help define a VAI cutoff with better efficacy to detect those with CAC >0 and presence of plaque.

Strengths of this study include the use of CT imaging to measure VAT and coronary plaque, which permitted correlation of VAI with the gold-standard technique. There were a few limitations. We recruited for a population with increased VAT as per protocol, which did not allow us to test VAI among those with lower amounts of VAT. We did not have a matched population of persons without HIV for comparison, which would be important to determine whether there are HIV-specific cutoffs. The VAI is a sex-specific formula, and there were few women in the study to try and understand sex-related differences in the correlations; however, the equation was designed to include sex as a key factor. In addition, increased proportions of other races would be important to include. The sample size in the current study was small and based on a convenience sample from participants in the RCT. Larger studies are needed to help us understand how VAI can be used among the broader HIV population and to help us discern risk based on sex, race, and HIV serostatus. Aside from its potential use to assess CVD risk, the utility of VAI in predicting CV events would be important to investigate as well.

Indeed, a large portion of PWH demonstrate subclinical atherosclerosis despite effective virological control on ART. The

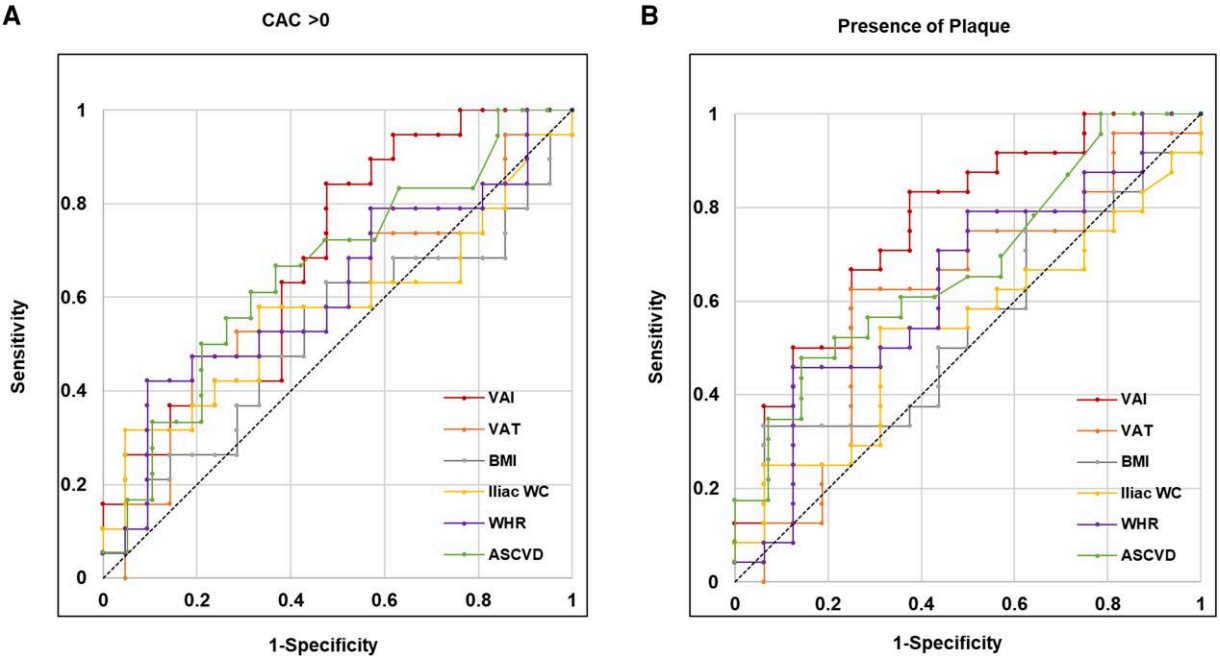

Figure 2. Receiver operating characteristic curves for body composition and cardiovascular disease risk indices with CAC >0 (*A*) and presence of any plaque (calcified, noncalcified, or mixed) (*B*). Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAC, coronary artery calcium score; VAI, visceral adiposity index; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist-to-hip ratio.

pathogenesis leading to increased CVD risk among PWH compared to persons without HIV remains unknown and could be related to adiposopathy. VAI could be used as an early clinical biomarker for subclinical disease in HIV, placing focus on CVD-preventive efforts for the mitigation of future cardiovascular events. These data highlight VAI as an emerging marker for CVD among PWH. Additional studies are needed to determine relevant VAI cutoffs for this to be employed practically in the clinical setting by the provider.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Data availability. Datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Disclaimer. The funding sources had no role in the design of the study, data analysis, or writing of the manuscript.

Financial support. This work was supported by the National Institutes of Health (grant/award numbers R01 DK49302 to S. K. G. and G. K. A.; K23 HL136262 and R01 HL151293 to S. S.; K24 HL103845 to G. K. A.; and P30 DK040561 to the Nutrition and Obesity Research Center at Harvard).

Potential conflicts of interest. S. S. was the recipient of a Gilead Sciences Research Scholars award. M. T. L. has received research funding from KOWA, MedImmune, AstraZeneca, Ionis, and Johnson & Johnson Innovation. S. K. G. has received research funding from KOWA, Gilead, ViiV, and Theratechnologies; has received consulting fees from Theratechnologies and ViiV; and is a member of the scientific advisory board of Marathon Asset Management, all unrelated to the present work. All other authors report no potential conflicts.

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