HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2023 March 01.

Published in final edited form as:

AIDS. 2022 March 01; 36(3): 399–407. doi:10.1097/QAD.0000000000003125.

Assessment of Coronary Inflammation in Antiretroviral Treated People Living with HIV Infection and Active HIV/HCV Co-Infection

Jean JEUDY, MD[1], **Pratik PATEL, MD**[2,*], **Nivya GEORGE, MS, MSc**[3,*], **Shana BURROWES, MPH, PhD**[4], **Jennifer HUSSON, MD, MPH**[3,5], **Joel CHUA, MD**[3,5], **Lora CONN, CCRC**[3], **Robert G. WEISS, MD**[6], **Shashwatee BAGCHI, MD, MS**[3,5]

[1]University of Maryland School of Medicine, Department of Diagnostic Radiology and Nuclear Medicine, Baltimore, Maryland

[2]Department of Radiology, University of Florida College of Medicine, Gainesville, Florida

[3]Department of Medicine, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, Maryland

[4]Department of Medicine, Section of Infectious Diseases, Boston University School of Medicine, Boston, Massachusetts

[5]Department of Medicine, Division of Infectious Diseases, University of Maryland School of Medicine, Baltimore, Maryland

[6]Department of Medicine, Division of Cardiology, Johns Hopkins School of Medicine, Baltimore, Maryland

Abstract

OBJECTIVE—Persons living with HIV (PLWH) and co-infected with hepatitis C (PLWH+HCV) have increased risk of cardiovascular disease (CVD). Peri-coronary inflammation, measured by fat attenuation index (FAI) on coronary CT angiography (CCTA), independently predicts cardiovascular risk in the general population but has not been studied in the PLWH+HCV population. We tested whether peri-coronary inflammation is increased in PLWH or PLWH+HCV, and whether inflammation changes over time.

DESIGN—Cross-sectional analysis to determine FAI differences among groups. Longitudinal analysis in PLWH to assess changes in inflammation over time.

METHODS—Age- and sex-matched seropositive groups (PLWH and PLWH+HCV) virologically suppressed on antiretroviral therapy (ART), HCV viremic, and without prior CVD and matched controls underwent CCTA. Peri-coronary FAI was measured around the proximal right coronary

Corresponding Author: Shashwatee Bagchi, MD, MS, Department of Medicine, Division of Infectious Diseases and Institute of Human Virology, University of Maryland School of Medicine, 725 West Lombard Street, N359, Baltimore, MD 21201, sbagchi@som.umaryland.edu.

*:Authors contributed equally to the manuscript work.

Conflict of Interest: None of the authors has any conflict of interest related to the preparation, analysis and submission of this manuscript. No author has any financial disclosure to report related to this publication, as confirmed by each one individually.

artery (RCA) and left anterior descending artery (LAD). Follow-up CCTA was performed in 22 PLWH after 20.6–27.4 months.

RESULTS—101 participants (48 women) were studied (60 PLWH, 19 PLWH+HCV and 22 controls). In adjusted analyses, peri-coronary FAI did not differ between seropositive groups and controls. Low attenuation coronary plaque was significantly less common in seropositive groups compared to controls (LAD, p=0.035; and RCA, p=0.017, respectively). Peri-coronary FAI values significantly progressed between baseline and follow-up in PLWH (RCA: p=0.001, LAD: p=<0.001).

CONCLUSIONS—PLWH and PLWH+HCV without history of CVD do not have significantly worse peri-coronary inflammation, assessed by FAI, compared to matched controls. However, peri-coronary inflammation in mono-infected PLWH significantly increased over approximately 22 months. FAI measures may be an important imaging biomarker for tracking asymptomatic CVD progression in PLWH.

Keywords

atherosclerosis; coronary artery disease; coronary computed tomography angiography (CCTA); HIV infection; Hepatitis C; peri-coronary inflammation; epicardial adipose tissue (EAT)

INTRODUCTION

Persons living with HIV (PLWH) and potentially those co-infected with hepatitis C virus (HCV) infection, are at increased risk of cardiovascular disease (CVD), independent of conventional cardiovascular risk factors [1–4]. Traditional CVD risk factors remain important contributors to increased CVD in HIV, HCV and HIV/HCV infections, but other potential factors include: use of older antiretroviral regimens or their legacy effects and persistent functional immunosuppression in HIV, increased systemic and local inflammation and cytokine imbalances in all three, and vascular invasion and liver damage particularly in HCV with or without cirrhosis and consequent metabolic perturbances, which may be exacerbated in HIV/HCV co-infection [5–15]. Ultimately, HIV, HCV and atherosclerosis are all inflammatory conditions [16–18].

Our ability to elucidate and target pathogenic mechanisms contributing to increased CVD risk are hampered by lack of robust indices that accurately measure coronary vascular inflammation. Increased serum biomarkers of inflammation, such as high-sensitivity C-reactive protein (hs-CRP), are associated with the development of atherosclerotic cardiovascular disease (ASCVD) but do not directly quantify the spatially-heterogeneous process of coronary atherogenesis [19,20]. Coronary calcium score was the only established noninvasive imaging biomarker with predictive value in primary prevention, but it describes nonreversible structural changes of the vascular wall and is not altered by interventions that reduce CVD risk [21]. Epicardial adipose tissue (EAT) is a subtype of visceral adipose tissue that is metabolically active, a source of inflammatory cytokines, and increased among PLWH which in theory, can contribute to local atherosclerosis and cardiovascular risk, especially in PLWH [22,23].

Noninvasive imaging of coronary inflammation has been described and validated by calculating the peri-coronary fat attenuation index (FAI) using coronary computed angiography (CCTA) in patients being referred for clinical indications, was found to independently predict cardiovascular risk in the general population, and perivascular FAI changes dynamically responded to local plaque rupture in patients with acute coronary syndrome (ACS) after percutaneous coronary intervention [24,25]. However, this novel imaging metric has been assessed in only one cross-sectional study in PLWH but without reporting comparison to controls [26] and not in those with HIV/HCV co-infection who are at higher risk of CVD than uninfected counterparts. In addition, FAI has not been evaluated in individuals asymptomatic for CVD.

Our study had two goals: 1) to assess whether peri-coronary inflammation is increased in PLWH with and without active HCV infection as compared to matched seronegative (non-HIV and non-HCV) controls and 2) to investigate whether peri-coronary fat inflammation changed over time. We hypothesized that peri-coronary fat inflammation is increased in PLWH with and without HCV infection compared to matched controls, and that peri-coronary fat inflammation progressed in PLWH without HCV co-infection over time.

METHODS

Study Participants

Adult patients from University of Maryland and other Baltimore clinics were prospectively enrolled in an IRB approved research study (HP-00074189) that included age- and sex-matched PLWH alone (mono-infected) and PLWH co-infected with HCV (co-infected) as part of an ongoing observational cohort. Our study included 60 mono-infected adults and 19 co-infected on stable antiretroviral therapy (ART) for at least 6 months, virologically suppressed at time of study entry, without prior history of ASCVD and low traditional risk factors for CVD. Twenty-two adults seronegative for HIV and HCV and age- and sex-matched to seropositive study participants with otherwise identical inclusion/exclusion criteria were prospectively enrolled. HIV infection was defined by confirmed HIV antibody or antigen/antibody result. HCV infection was defined by confirmed HCV antibody result, all had HCV detectable serum HCV quantitative ribonucleic acid levels and were treatment naïve for any type of HCV therapy. Controls were confirmed negative for both HIV and HCV infections. Further elaboration on recruitment is detailed in the online Supplement.

Those with unstable coronary syndromes or any symptoms suggestive of acute coronary syndromes, systolic blood pressure >160 mmHg, low density lipoprotein cholesterol (LDL-c) >160 mg/dL, poorly controlled diabetes defined as need for anti-glycemic therapies and/or HbA1c >7%, hemoglobin <7 g/dl, or creatinine clearance<45 mL/min were excluded. Other exclusion criteria are detailed in the online Supplement.

Study Procedures

Initial baseline evaluation consisted of history, physical exam, and blood draw. Eligible participants underwent a baseline CCTA, and follow-up visits consisted of serial histories to monitor changes in sociodemographic and clinical status including medication changes,

blood draws and a final CCTA. Sociodemographic, clinical, and medical histories were obtained directly from participant interviews and supplemented by chart reviews of electronic medical records (EPIC, CareEverywhere, CRISP). Laboratory assessments for all assays in this study were sent to Labcorps reference laboratory for testing.

CT Imaging protocol

Prior to scanning, heart rate and blood pressure monitoring were performed. Nitroglycerin (sublingual, 0.4 – 0.8 mg) was administered after initial tomographic scouting. Prospectively ECG-triggered axial acquisition for calcium scoring study was performed and followed by intravenous administration of 5–15 mg of metoprolol if the participant's heart rate was above 65 bpm. CCTA (retrospectively ECG-gated or prospectively ECG-triggered scan) was acquired using a third-generation dual source CT scanner (SOMATOM Force, Siemens Medical Solutions, Forchheim, Germany) scanned from September 2017 to June 2021. CCTA acquisition was performed with a collimation of $2 \times 192 \times 0.6$ mm, a gantry rotation time of 0.25 s, and automatic exposure control enabling adjustment of tube voltage and tube current based on body size. Images were acquired at a section thickness of 0.5 mm and increment of 0.25 mm. All scans were performed using a single inspiratory breath hold. Iohexol (Omnipaque 350 mg/mL, GE Healthcare, Buckinghamshire, UK) was administered into an antecubital vein via an 18–20 gauge intravenous catheter after test bolus acquisition. A volume of 80 to 100 mL at a flow rate of 6 mL/s was used for image acquisition followed by 50 mL of normal saline.

Images were transferred to a central server for post processing and analysis. Curved multiplanar and 3D volume rendered reconstructions were created for interpretation. Coronary analysis was performed per coronary segment, using the modified 15-segment model of the American Heart Association [27]. Quantitative plaque analysis was performed using validated software (Aquarius iNtuition; TeraRecon Inc., USA), by two radiologists (P.P. and J.J.) who were blinded to participant serostatus. The senior radiologist with over 15 years of experience (J.J.) performed quality control, supervision, and assurance of the analyses. Quantitative plaque measurements were conducted in all coronary segments with or without coronary plaques. Measurements of proximal and distal reference sites at normal or nearly normal vessel locations were obtained adjacent to the plaque. Mean luminal diameter, luminal area, and diameter stenosis were measured. Luminal diameter stenosis was calculated as the minimal luminal diameter divided by the mean of the luminal diameters of the proximal and distal reference sites.

If coronary plaque was present, the size and composition of plaque were qualitatively noted. The presence of high-risk plaque features, including positive remodeling (remodeling index > 1.1), low CT attenuation (presence of non-calcified plaque with CT attenuation <60 HU), napkin-ring sign (presence of a central area of low CT attenuation in contact with the lumen with ring-like higher attenuation plaque tissue surrounding this central area) and spotty calcium (size of calcium: <3 mm diameter, length < 1.5 of vessel diameter, width < 2/3 of vessel diameter) were also recorded [28,29]. Unevaluable segments due to image degradation, noise-related blurring, or severe motion artifact were not evaluated.

FAI Measurements

Peri-coronary fat attenuation was measured around the proximal right coronary artery (RCA) and left anterior descending artery (LAD) and defined as the mean attenuation of all adipose-containing voxels between −190 to −30 Hounsfeld units (HU) obtained from the outer wall of the vessel within a radius equal to the diameter of the vessel. A total length of 40mm from the proximal portion of the RCA and LAD was measured. By convention, the proximal 10 mm of the RCA was excluded to limit artifact from the aortic wall [24].

At time of analysis, 22 of the initial 60 mono-infected completed their follow-up CCTA after median of 21.8 months. Quantitative FAI measurements were repeated and compared to baseline values. FAI measurements were not evaluable in RCA for two participants.

Statistical Analysis

We performed a cross-sectional analysis to determine differences in FAI among groups, and a longitudinal analysis in mono-infected PLWH to assess changes in per-coronary inflammation over time.

We summarized and compared demographic features, behavioral, clinical indicators and radiological features among serostatus groups: mono-infected, co-infected, and HIV and HCV negative. Summary statistics were reported using mean ± standard deviation (SD) or median with first and third quartiles as indicated based upon data distribution. For continuous variables, one-way ANOVA or Kruskal Wallis test was used to examine differences among groups based on normality of data distribution. For categorical variables, Chi-square test or Fisher's Exact test was used as appropriate to examine significant differences. Demographic features, behavioral and clinical indicators were compared between mono-infected and controls. For continuous variables, an independent t test or a non-parametric Mann-Whitney U test was used to examine the difference between groups as indicated. For categorical variables, Chi-square test or Fisher's Exact test was used as appropriate to examine the significant difference.

The primary endpoint was mean FAI and it was examined further in the adjusted models. A multivariable regression analysis was performed to evaluate the association between serostatus and mean FAI adjusting for potential confounders: age, sex, race, LDL-c, lipid lowering medication use and body mass Index (BMI) (<30 and >=30). Adjusted regression coefficients were reported with 95% Confidence interval. The residual plots were examined and checked for normality.

A sensitivity analysis was performed for mean FAI values after removing six patients who had extreme BMI values (BMI >=40) in the control group. This resulted in study groups with comparable mean BMI values and reduced the confounding effect of BMI when assessing perivascular fat measure.

We examined the change in mean FAI values in RCA and LAD coronary arteries separately from first to second visit using Wilcoxon signed rank test. We investigated associations between baseline, follow-up, and the change from baseline to follow-up of hs-CRP levels and between integrase strand transfer inhibitor (INSTI) with FAI progression in mono-

infected using adjusted models. The associations between virologic control and other ART classes with FAI progression were considered but not possible. Adjusted regression coefficients were reported with 95% Confidence interval. Statistical significance was defined as $P \leq 0.05$. Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). More detailed description of Statistical Analysis can be found in the online Supplement.

RESULTS

Baseline Characteristics of Study groups

A total of 101 participants (48 women) were enrolled in the study - 60 mono-infected, 19 co-infected, and 22 controls. All mono-infected and co-infected participants remained virologically suppressed at study follow-up visits. Baseline sociodemographic, behavioral, and clinical indicators are shown in Table 1 (comparing three study groups) and Supplementary Table 1 (comparing mono-infected and controls only). No significant baseline differences in age, sex, smoking status, blood pressure, use of anti-hypertensive medications, lipid parameters, and baseline ASCVD risk scores were seen between groups. Mono-infected and co-infected groups were predominantly African American, with significantly higher rates of past illicit drug use compared to controls. In contrast, controls had statistically higher BMI and current alcohol use compared to mono-infected and co-infected groups. After removing the six most obese participants from the control group, BMIs were comparable between study groups: (means and SD) 27.3±6.1, 28.7±4.3 and 28.4±5.3 for mono-infected, co-infected, and controls, respectively.

Coronary Plaque Characteristics

Quantitative plaque analysis was performed in 101 participants and summarized in Table 2 and Supplementary Table 2. The majority of participants had a zero calcium score with no significant differences in prevalence of non-zero calcium scores among groups. The presence of spotty calcification or napkin ring sign was uncommon in all groups. Presence of low attenuation plaque was significantly higher in controls compared to mono-infected and co-infected (RCA and LAD distributions, p=0.035, and p=0.017, respectively).

Fat Attenuation Index Values and Viral Infection Serostatus

In unadjusted analyses, mean FAI was significantly lower in controls compared to mono-infected and co-infected and mono-infected alone for both RCA and LAD distributions (Table 2 and Supplementary Table 2). After adjusting for age, sex, race, LDL-c level, use of lipid lowering medication and obesity (defined as BMI=>30), there was no association between mean FAI and mono-infected versus controls or between mono-infected and co-infected versus controls (Tables 3a and 3b). There was a significant association between HIV/HCV co-infection alone and mean RCA FAI but not for LAD FAI (Table 3c). To minimize potential confounding of obesity on the intergroup FAI differences, we performed additional sensitivity analyses whereby the six most obese participants were removed from the control group (Supplementary Tables 3a and 3b). After adjusting for potential confounders, the sensitivity analyses demonstrated no association between any serostatus

group combination and mean FAI in either LAD or RCA (Supplementary Tables 4a–d), consistent with the adjusted primary analyses (Tables 3a and 3b).

Change in Fat Attenuation Index Values in Persons Living with HIV on follow up

Longitudinal follow-up evaluation in 22 mono-infected participants (median = 21.8 months) demonstrated progression of mean RCA FAI values between baseline and follow-up (−86.38 at baseline, vs −85.11 on follow-up, p=0.001) despite maintained virologic suppression in all participants and 13–18% being on statins and other lipid-lowering medications, respectively. Similar progression of FAI values were observed in the LAD distribution (−86.55 vs −84.77, p<0.001) (Table 4). There were no associations found between FAI progression and INSTI use or baseline, follow-up or change in hs-CRP values (Supplementary Table 5).

DISCUSSION

In this study, we found that asymptomatic PLWH and persons co-infected with HIV and active HCV stable on ART had no significant differences in FAI values compared to controls, after adjusting for potential confounders. However, mono-infected and co-infected participants had less prevalence of low attenuation plaques compared to controls. It is noteworthy that the control group had higher rates of statin and lipid-lowering medication use as well as higher mean BMI compared to the HIV and/or HCV co-infected groups, suggesting an unmeasured higher baseline CVD risk not identified by baseline ASCVD risk score or other traditional CV risk factors captured. The potentially higher unmeasured CVD risk of the controls may have depreciated the association between serostatus and FAI in our study. We attempted to minimize the potential confounding of BMI between the association of serostatus and mean FAI in sensitivity analyses and found no association between HIV with or without HCV with peri-coronary fat inflammation as compared to controls in those analyses.

HIV associated ASCVD is a substantial public health problem, but the underlying mechanisms remain incompletely elucidated. Evidence suggests that inflammation and immune activation may be causative factors beyond traditional CVD risk factors [5,10], and PLWH on stable ART with immune reconstitution still experience higher rates of acute myocardial infarction compared to persons without HIV [1,4]. HCV infection has also been implicated as an independent risk factor for the development of subclinical and clinical CVD [6,14,15,29].

Plasma markers such as hs-CRP and other pro-inflammatory markers assess systemic inflammation, but do not directly measure vascular inflammation [19,20] and they have been variably associated with CVD in patients living with HIV or HCV [30–32].

Evidence from recent randomized clinical trials demonstrated an association of vascular inflammatory mediators with coronary artery disease [33] CCTA provides a means of mapping inflammatory changes to both EAT and peri-coronary adipose tissue as independent markers of coronary risk. Noninvasive imaging of coronary artery inflammation has been previously described and validated by calculating the peri-coronary fat attenuation index (FAI) using CCTA [24]. The Cardiovascular RISk Prediction using Computed

Tomography (CRISP-CT) study demonstrated that FAI values could predict cardiac and all-cause mortality endpoints in two large independent prospective cohorts [25]. Importantly, perivascular FAI changes dynamically responded to local plaque rupture in patients with ACS after percutaneous coronary intervention [24]. In addition, among individuals who were recommended to initiate treatment with statins or aspirin after CCTA (measured before initiation of the new treatment), the perivascular FAI was no longer predictive of cardiac mortality compared to retained predictive value of high FAI values among those who were not recommended to initiate preventive measures, suggesting that the risk identified by the perivascular FAI could be modifiable with optimum medical therapy [25].

CAC scores were not significantly different among groups in our study. In the Multicenter AIDS Cohort Study (MACS) [35] a multiethnic cohort of HIV seropositive and HIV-seronegative men, PLWH receiving at least eight years of ART were found to have significantly lower CAC compared with controls. In our study, the majority of study participants had zero CAC score, with no difference among serogroups. When considering CAC as a classic cardiovascular risk biomarker, the development of coronary calcification is a consequence of chronic coronary plaque rupture, organization, and remodeling [36]. As such, CAC values do not reflect early peri-coronary inflammation which manifests as inflamed EAT, perivascular inflammation and low attenuation plaque. Use of CAC as a biomarker only partially considers the full pathophysiology of coronary inflammation and potentially underestimates the severity of cardiovascular risk that would be revealed using FAI.

Previous meta-analysis of 1229 asymptomatic HIV-positive patients receiving ART demonstrated a threefold higher prevalence of low attenuation plaque on CCTA, compared with HIV-negative controls, raising the concern for accelerated atherosclerosis among PLWH [34]. To our knowledge, there is only one study assessing FAI in PLWH using CCTA for clinical indications [26]. Our study is the first to compare FAI among mono-infected and co-infected PLWH and controls. In addition, ours is the first to evaluate FAI in persons asymptomatic for CVD and without prior CVD, and the first to evaluate FAI changes in PLWH over time.

Twenty-two mono-infected PLWH who received repeat imaging with CCTA after a median follow up of 21.8 months showed progression of mean FAI values (less negative attenuation) in RCA and LAD distributions between baseline and follow-up scans despite maintained virologic suppression and a notable percentage on statins or lipid-lowering medications. Such findings are consistent with atherosclerotic progression involving mechanistic pathways beyond lipid-induced inflammation alone in ART-suppressed, immune reconstituted mono-infected participants (Table 4). These findings demonstrate for the first time that adverse changes in coronary FAI can occur in less than two years in low-risk, asymptomatic PLWH and highlight the importance of monitoring peri-coronary inflammation longitudinally even in those presumed to be low-risk for cardiovascular disease in PLWH.

Our study has some important strengths. To our knowledge, this was the first study to evaluate coronary inflammation assessed by FAI values in asymptomatic people among

mono-infected and co-infected PLWH, and the first to compare their values to those of controls. Asymptomatic persons are ideal for targeting primary CVD prevention measures, and HIV and possibly HIV/HCV co-infected people are at higher risk of experiencing CVD events compared to the general population thus representing a target group of high interest for CVD prevention. Additionally, this is the first study to report progression of peri-coronary fat inflammation in asymptomatic PLWH over time. This is especially important in the context of an aging HIV population with 51% of PLWH and almost 17% of new HIV infections in 2018 being in adults 50 years or older [37] and most likely to succumb from chronic diseases of aging rather than HIV-related conditions. In this context, we demonstrated an important finding of the progression of peri-coronary fat inflammation among PLWH well-controlled on stable ART in only 20.6–27.4 months.

Our study had some notable limitations. Our modest sample size may have lacked sufficient power to detect associations between serogroups and peri-coronary fat inflammation, as assessed by mean FAI values. There may be residual confounding from unknown or unmeasured factors (legacy effects of delayed or lack of ART, use of older ART regimens, CD4 cell count nadir) and/or baseline differences between study groups that cannot be fully corrected using multivariable regression analyses. Ideally, we would have matched for race at enrollment, but we attempted to minimize the effect of race on inflammation by adjusting for it in the multivariable analyses. Future studies in larger cohorts are needed to further investigate if peri-coronary fat inflammation differs in sub-populations of PLWH (women, elderly), in those with HCV mono-infection, and longitudinal studies are needed in HCV mono-infected and HIV/HCV co-infected to assess how peri-coronary inflammation changes with HCV treatment and over time in these populations. In addition, studies are needed that explore whether the residual CV risk detected by peri-coronary FAI can be reduced using targeted anti-inflammatory interventions beyond statins. Assessment of peri-coronary FAI could be a useful tool in tracking peri-coronary inflammation for investigations into the immunopathogenesis of evolving coronary inflammation, early atherosclerosis and CVD risk and also serve as an imaging biomarker for preventive and therapeutic intervention trials in CVD. Over time, FAI could potentially be used in clinical practice for risk-stratification in certain CVD-risk groups in HIV and/or HCV populations.

CONCLUSION

Our study findings suggest that asymptomatic PLWH and those living with both HIV and HCV do not have significantly worse peri-coronary inflammation as assessed by perivascular FAI compared to asymptomatic people without HIV or HCV infection. However, peri-coronary inflammation among mono-infected participants increased significantly in less than two years, highlighting the importance of monitoring FAI longitudinally and investigating CVD preventive measures in the current aging HIV population perhaps using FAI measurements as a therapeutic biomarker endpoint.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

The following authors contributed to the conception of study design (JJ, S Burrowes, RGW, S Bagchi), data collection (JJ, PP, JH, JC, LC, S Bagchi), analysis and interpretation of data (JJ, NG, S Burrowes, RGW, S Bagchi), and critical revision of the manuscript (all authors). We thank the Institute of Human Virology, Division of Clinical Care & Research at the University of Maryland School of Medicine for providing supplemental support of the project.

Funding Source:

The preparation and publication of the manuscript was supported by University of Maryland, Baltimore, Institute for Clinical & Translational Research (ICTR) and the National Center for Advancing Translational Sciences (NCATS) Clinical Translational Science Award (CTSA)(UL1TR003098), National Heart, Lung, and Blood Institute of the National Institutes of Health,(5K23HL133358), and National Institutes of Health (HL125059, AG063661).

REFERENCES

1. Currier JS, Taylor A, Boyd F, Dezii CM, Kawabata H, Burtcel B, et al. Coronary heart disease in HIV-infected individuals. J Acquir Immune Defic Syndr 2003; 33:506–512. [PubMed: 12869840]
2. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol 2013; 10:553–562. [PubMed: 23817321]
3. Lee KK, Stelzle D, Bing R, Anwar M, Strachan F, Bashir S, et al. Global burden of atherosclerotic cardiovascular disease in people with hepatitis C virus infection: a systematic review, meta-analysis, and modelling study. Lancet Gastroenterol Hepatol 2019; 4:794–804. [PubMed: 31377134]
4. Shah ASV, Stelzle D, Lee KK, Beck EJ, Alam S, Clifford S, et al. Global Burden of Atherosclerotic Cardiovascular Disease in People Living With HIV: Systematic Review and Meta-Analysis. Circulation 2018; 138:1100–1112. [PubMed: 29967196]
5. Triant VA. HIV infection and coronary heart disease: an intersection of epidemics. J Infect Dis 2012; 205 Suppl 3:S355–61. [PubMed: 22577208]
6. Babiker A, Jeudy J, Kligerman S, Khambaty M, Shah A, Bagchi S. Risk of Cardiovascular Disease Due to Chronic Hepatitis C Infection: A Review. J Clin Transl Hepatol 2017; 5:343–362. [PubMed: 29226101]
7. Tan BK, Chalouni M, Ceron DS, Cinaud A, Esterle L, Loko MA, et al. Atherosclerotic Cardiovascular Events in Patients Infected With Human Immunodeficiency Virus and Hepatitis C Virus. Clin Infect Dis 2021; 72:e215–e223. [PubMed: 32686834]
8. Boccara F, Lang S, Meuleman C, Ederhy S, Mary-Krause M, Costagliola D, et al. HIV and coronary heart disease: time for a better understanding. J Am Coll Cardiol 2013; 61:511–523. [PubMed: 23369416]
9. Burrowes S, Cahill P, Kottilil S, Bagchi S. Contribution of antiretroviral therapy to cardiovascular disease risk in HIV-infected patients. Future Virol 2016; 11:509–527.
10. Hsue PY, Deeks SG, Hunt PW. Immunologic basis of cardiovascular disease in HIV-infected adults. J Infect Dis 2012; 205 Suppl 3:S375–82. [PubMed: 22577211]
11. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med 2011; 62:141–155. [PubMed: 21090961]
12. Babiker A, Hassan M, Muhammed S, Taylor G, Poonia B, Shah A, et al. Inflammatory and cardiovascular diseases biomarkers in chronic hepatitis C virus infection: A review. Clin Cardiol 2020; 43:222–234. [PubMed: 31785111]
13. Heydtmann M, Adams DH. Chemokines in the immunopathogenesis of hepatitis C infection. Hepatology 2009; 49:676–688. [PubMed: 19177577]
14. Negro F Facts and fictions of HCV and comorbidities: steatosis, diabetes mellitus, and cardiovascular diseases. J Hepatol 2014; 61:S69–78. [PubMed: 25443347]
15. Cacoub P, Saadoun D. Extrahepatic Manifestations of Chronic HCV Infection. N Engl J Med 2021; 384:1038–1052. [PubMed: 33730456]
16. Libby P Inflammation in atherosclerosis. Nature 2002; 420:868–874. [PubMed: 12490960]

17. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med 2017; 377:1119–1131. [PubMed: 28845751]

18. Lo J, Plutzky J. The biology of atherosclerosis: general paradigms and distinct pathogenic mechanisms among HIV-infected patients. J Infect Dis 2012; 205 Suppl 3:S368–74. [PubMed: 22577210]

19. Lee R, Margaritis M, Channon KM, Antoniades C. Evaluating oxidative stress in human cardiovascular disease: methodological aspects and considerations. Curr Med Chem 2012; 19:2504–2520. [PubMed: 22489713]

20. Margaritis M, Antonopoulos AS, Digby J, Lee R, Reilly S, Coutinho P, et al. Interactions between vascular wall and perivascular adipose tissue reveal novel roles for adiponectin in the regulation of endothelial nitric oxide synthase function in human vessels. Circulation 2013; 127:2209–2221. [PubMed: 23625959]

21. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004; 291:210–215. [PubMed: 14722147]

22. Shimabukuro M, Hirata Y, Tabata M, Dagvasumberel M, Sato H, Kurobe H, et al. Epicardial adipose tissue volume and adipocytokine imbalance are strongly linked to human coronary atherosclerosis. Arterioscler Thromb Vasc Biol 2013; 33:1077–1084. [PubMed: 23471228]

23. Lo J, Abbara S, Rocha-Filho JA, Shturman L, Wei J, Grinspoon SK. Increased epicardial adipose tissue volume in HIV-infected men and relationships to body composition and metabolic parameters. AIDS 2010; 24:2127–2130. [PubMed: 20588167]

24. Antonopoulos AS, Sanna F, Sabharwal N, Thomas S, Oikonomou EK, Herdman L, et al. Detecting human coronary inflammation by imaging perivascular fat. Sci Transl Med 2017; 9. doi:10.1126/scitranslmed.aal2658

25. Oikonomou EK, Marwan M, Desai MY, Mancio J, Alashi A, Hutt Centeno E, et al. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. Lancet 2018; 392:929–939. [PubMed: 30170852]

26. Senoner T, Barbieri F, Adukauskaite A, Sarcletti M, Plank F, Beyer C, et al. Coronary atherosclerosis characteristics in HIV-infected patients on long-term antiretroviral therapy: insights from coronary computed tomography-angiography. AIDS 2019; 33:1853–1862. [PubMed: 31259763]

27. van Velzen JE, de Graaf FR, de Graaf MA, Schuijf JD, Kroft LJ, de Roos A, et al. Comprehensive assessment of spotty calcifications on computed tomography angiography: Comparison to plaque characteristics on intravascular ultrasound with radiofrequency backscatter analysis. J Nucl Cardiol 2011; 18:893. [PubMed: 21769702]

28. Puchner SB, Liu T, Mayrhofer T, Truong QA, Lee H, Fleg JL, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. J Am Coll Cardiol 2014; 64:684–692. [PubMed: 25125300]

29. Osibogun O, Ogunmoroti O, Michos ED, Spatz ES, Olubajo B, Nasir K, et al. HIV/HCV coinfection and the risk of cardiovascular disease: A meta-analysis. J Viral Hepat 2017; 24:998–1004. [PubMed: 28502092]

30. Worm SW, Hsue P. Role of biomarkers in predicting CVD risk in the setting of HIV infection? Curr Opin HIV AIDS 2010; 5:467–472. [PubMed: 20978389]

31. Huang C-F, Hsieh M-Y, Yang J-F, Chen W-C, Yeh M-L, Huang C-I, et al. Serum hs-CRP was correlated with treatment response to pegylated interferon and ribavirin combination therapy in chronic hepatitis C patients. Hepatol Int 2010; 4:621–627. [PubMed: 21063486]

32. Oguz A, Atay AE, Tas A, Seven G, Koruk M. Predictive role of acute phase reactants in the response to therapy in patients with chronic hepatitis C virus infection. Gut Liver 2013; 7:82–88. [PubMed: 23424009]

33. Yuvaraj J, Cheng K, Lin A, Psaltis PJ, Nicholls SJ, Wong DTL. The Emerging Role of CT-Based Imaging in Adipose Tissue and Coronary Inflammation. Cells 2021; 10. doi:10.3390/cells10051196

34. D'Ascenzo F, Cerrato E, Calcagno A, Grossomarra W, Ballocca F, Omedè P, et al. High prevalence at computed coronary tomography of non-calcified plaques in asymptomatic HIV patients treated with HAART: a meta-analysis. Atherosclerosis 2015; 240:197–204. [PubMed: 25797313]

35. Kingsley LA, Cuervo-Rojas J, Muñoz A, Palella FJ, Post W, Witt MD, et al. Subclinical coronary atherosclerosis, HIV infection and antiretroviral therapy: Multicenter AIDS Cohort Study. AIDS 2008; 22:1589–1599. [PubMed: 18670218]

36. van der Wal AC. Coronary artery pathology. Heart 2007; 93:1484–1489. [PubMed: 17934012]

37. Centers for Disease Control and Prevention. HIV and Older Americans. Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. https://www.cdc.gov/hiv/group/age/olderamericans/index.html (accessed 25 Jul2021).

Table 1:

Sociodemographic and Clinical Characteristics of Study Population

Variables	HIV mono-infected n=60 (59.4%)	HIV and HCV Co-infected n=19 (18.8%)	HIV and HCV Negative n=22 (21.8%)	P value
Sociodemographic factors				
Sex at Birth, n(%)				
Female	28 (46.7%)	7 (38.9%)	13 (61.9%)	0.323 *
Age at enrollment (years) Mean±SD	51.53±9.31	53.22±6.04	53.14±5.00	0.612 #
Race, n (%)				
Black/African American	49 (83.1%)	16 (88.9%)	12 (57.1%)	**0.035** **
White	10(16.9%)	2 (11.1%)	9 (42.9%)	
Education (n (%))				
High School Education or Less	48 (80.0%)	17 (94.4%)	8 (38.1%)	**<0.001** *
Post High School Education	12 (20.0%)	1 (5.6%)	13 (61.9)	
Income, n (%)				
< $25,000	40 (66.7%)	16 (88.9%)	3 (14.3%)	**<0.001** *
Behavioral Indicators, n(%)				
Cigarette smoker				
Current	24 (40.0%)	11 (61.1%)	5 (23.8%)	0.060 *
Past	29 (53.7%)	13 (81.3%)	6 (33.3%)	**0.019** *
Alcohol use				
Current	32 (53.3%)	4 (22.2%)	18 (85.7%)	**<0.001** *
Past	45 (84.9%)	14(82.4%)	9 (60.0%)	0.125 **
Illicit use				
Current	3 (5.0%)	1 (5.6%)	0(0%)	-
Past	17 (28.3%)	17 (94.4%)	1 (4.8%)	**<0.001** *
Clinical Indicators				
Duration of HIV Diagnosis, years, Mean±SD	17.95±9.31	16.78±6.29	-	0.619 €
ART Duration, years, Median (Q1, Q3)	5.50 (2.00,7.75)	7.00 (2.00,7.75)	-	0.478 €€
CD4 cell count/mm^3, Median (Q1, Q3)	692.00 (543.00,1030.00)	642.00 (440.25,869.00)	-	0.279 €€
Hepatitis B infected, n (%)	5 (8.3%)	2 (11.8%)	0 (0%)	0.286 **
Hepatitis B and C infected, n (%)	0 (0%)	2 (11.8%)	0 (0%)	-
Family History CVD, n(%)	19 (31.7%)	5 (27.8%)	11 (52.4%)	0.176 *
Baseline ASCVD Risk Score, Median (Q1, Q3)	0.05(0.02,0.09)	0.06(0.03,0.09)	0.05(0.03,0.12)	0.804 ¥
BMI, Mean±SD	27.26±6.10	28.91±4.23	33.43±9.59	**0.027** ##

Variables	HIV mono-infected n=60 (59.4%)	HIV and HCV Co-infected n=19 (18.8%)	HIV and HCV Negative n=22 (21.8%)	P value
Antihypertensive use, n(%)	22 (95.7%)	4 (100%)	11(100%)	-
Statin use, n (%)	8 (13.3 %)	0 (0%)	7 (33.3 %)	**0.013** **
Other lipid-lowering medication use, n (%)	9 (18.0%)	0 (0%)	6 (33.3%)	**0.029** **
Systolic blood pressure mm Hg, Mean±SD	124.63±16.90	130.06±19.03	128.43±20.26	0.457#
Total Cholesterol, mg/dL, Median (Q1, Q3)	183.00 (151.00,202.25)	161.00 (140.00,181.75)	177.00 (152.50,205.00)	0.108¥
HDL, mg/dL, Median (Q1, Q3)	51.00 (46.00,66.75)	50.00 (43.75,69.50)	49.00 (42.50,75.00)	0.811¥
LDL, mg/dL, Median (Q1, Q3)	101.50 (76.00, 122.00)	82.50 (65.25,101.50)	104.00 (76.00,125.50)	0.085¥
Triglycerides, mg/dL, Median (Q1, Q3)	94.50 (69.50,132.00)	104.00 (76.75,126.50)	72.00 (60.50,99.00)	0.195¥

ART-antiretroviral therapy; ASCVD- atherosclerotic cardiovascular disease; BMI- body mass index;

CVD- cardiovascular disease; HDL-high density lipoprotein; HCV- hepatitis C virus; HIV- human immunodeficiency virus; LDL-low density lipoprotein

*P value using Chi Square test.

**P value using Fisher's Exact test.

#p value using One-Way ANOVA.

##P value using Welch.

¥P value using Kruskal Walli's test.

€P value using Independent t test.

€€P value using Mann Whitney U test.

Table 2:

Coronary Plaque Features of Study Population

Variable	HIV mono-infected n=60 (59.4%)	HIV and HCV Co-infected n=19 (18.8%)	HIV and HCV Negative n=22 (21.8%)	p value
CAD prevalence (any plaque), n (%)				
0	44 (74.6%)	11 (57.9%)	15 (71.4%)	0.380 *
>0	15 (25.4%)	8 (42.1%)	6 (28.6%)	
CAD RADS, n (%)				
No Coronary Plaque	39 (65.0%)	9 (47.4%)	15 (68.2%)	0.525 **
1–24%	12 (20.0%)	7 (36.8%)	5 (22.7%)	
25–49%	5 (8.3%)	2 (10.5%)	0 (0%)	
>=50%	4 (6.7 %)	1 (5.3%)	2 (9.1%)	
Total >=50%	4 (6.7%)	1 (5.3%)	2 (9.1%)	1.000 **
<50%	56 (93.3%)	18 (94.7%)	20 (90.9%)	
Calcium Score, Median (Q1, Q3)	0 (0,14.58)	0 (0,80.60)	0 (0,17.3)	-
Calcium Score, n(%)				
0	38 (63.3%)	9 (47.4%)	15 (68.2%)	0.350 *
>0	22 (36.7%)	10 (52.6%)	7 (31.8%)	
RCA Mean FAI, Median (Q1,Q3)	−86.04 (−86.67, −85.18)	−86.37 (−87.00, −84.95)	−84.95 (−86.11, −84.07)	**0.037** ¥
LAD Mean FAI, Median (Q1,Q3)	−86.24 (−86.78, −85.48)	−85.86 (−86.24, −84.74)	−85.08 (−85.92, −83.96)	**0.001** ¥
RCA LAP, Median (Q1,Q3)	0.00 (0.00, 0.02)	0 .01 (0.00, 0.02)	0.01 (0.00, 0.04)	**0.035** ¥
LAD LAP, Median (Q1,Q3)	0.00 (0.00,0.01)	0.01 (0, 0.02)	0.02 (0.00, 0.03)	**0.017** ¥
Spotty calcification, n(%)				
0	50 (84.7%)	15 (78.9%)	19 (90.5%)	0.627 **
>0	9 (15.3%)	4 (21.1%)	2 (9.5%)	
Napkin ring sign, n (%)				
0	55 (93.2%)	18 (94.7%)	19 (90.5%)	0.866 **
>0	4 (6.8%)	1 (5.3%)	2 (9.5%)	

CAD - Coronary Artery Disease; CAD RADS- Coronary Artery Disease Reporting and Data System; FAI- Fat Attenuation Index; LAD- Left Anterior Descending artery; LAP- Low Attenuation 60 Plaque; RCA- Right Coronary Artery

* P value using Chi Square test.

** P value using Fisher's Exact test.

¥ P value using Kruskal Walli's test

Table 3:
Association of HIV and HIV/HCV Infection Serostatus and Fat Attenuation Index Values.

Table 3a: Persons Living with HIV and/or HCV (n=79) compared to those without HIV or HCV (n=22) Infections

Table 3b: Persons Living with HIV (n=60) compared to those without HIV or HCV (n=22) Infections

Table 3c: Persons Living with HIV and HCV (n=19) compared to those without HIV or HCV (n=22) Infections

Table 3d: Persons Living with HIV (n=60) compared to those with HIV and HCV (n=19) Infections.

	RCA Mean FAI		**LAD Mean FAI**	
Variable	**Beta Coefficient (95% Confidence Interval)**	**P value**	**Beta Coefficient (95% Confidence Interval)**	**P value**
HIV+ *and* HIV+/HCV+ vs HIV-/HCV-	−0.552 (−1.302, 0.197)	0.146	−0.500 (−1.205, 0.206)	0.163
Age	0.010 (−0.026,0.045)	0.593	0.017 (−0.017, 0.052)	0.325
Sex	−0.316 (−0.929, 0.298)	0.309	−0.288 (−0.864 ,0.289)	0.324
Race	−0.330 (−1.061, 0.402)	0.372	0.522 (−0.168, 1.213)	0.136
LDL-c level	−0.005 (−0.015, 0.005)	0.312	−0.005 (−0.015, 0.004)	0.267
Use of lipid lowering medication	0.266 (−0.495, 1.028)	0.488	0.097 (−0.648, 0.842)	0.796
BMI =>30	0.927 (0.284, 1.570)	**0.005**	0.765 (0.162, 1.368)	**0.014**

	RCA Mean FAI		**LAD Mean FAI**	
Variable	**Beta Coefficient (95% Confidence Interval)**	**P value**	**Beta Coefficient (95% Confidence Interval)**	**P value**
HIV+ vs HIV-/HCV-	−0.439 (−1.197, 0.319)	0.251	−0.543 (−1.178, 0.092)	0.093
Age	0.012 (−0.025, 0.048)	0.526	0.011 (−0.020, 0.043)	0.472
Sex	−0.236 (−0.916, 0.444)	0.489	−0.308 (−0.875, 0.259)	0.281
Race	−0.389 (−1.164,0.387)	0.320	0.618 (0.033, 1.268)	0.062
LDL-c level	−0.005 (−0.015, 0.006)	0.376	−0.003 (−0.012, 0.006)	0.457
Use of lipid lowering medication	0.201 (−0.555, 0.957)	0.596	0.211 (−0.453, 0.875)	0.528
BMI =>30	0.998 (0.266, 1.731)	**0.008**	0.840 (0.232, 1.449)	**0.008**

	RCA Mean FAI		**LAD Mean FAI**	
Variable	**Beta Coefficient (95% Confidence Interval)**	**P value**	**Beta Coefficient (95% Confidence Interval)**	**P value**
HIV+/HCV+ vs HIV-/HCV-	−1.648 (−2.983, −0.312)	**0.018**	−0.186 (−1.620, 1.249)	0.792

	RCA Mean FAI		LAD Mean FAI	
Variable	**Beta Coefficient (95% Confidence Interval)**	**P value**	**Beta Coefficient (95% Confidence Interval)**	**P value**
Age	0.076 (−0.033,0.185)	0.162	0.009 (−0.109, 0.127)	0.874
Sex	−0.668 (−1.716, 0.381)	0.202	−0.475 (−1.623,0.674)	0.403
Race	0.384 (−0.924, 1.693)	0.551	0.343 (−1.106, 1.793)	0.630
LDL-c level	−0.017 (−0.036, 0.033)	0.090	−0.009 (−0.031, 0.012)	0.381
Use of lipid lowering medication	−1.408 (−3.140, 0.324)	0.107	0.449 (−1.430, 2.328)	0.627
BMI =>30	0.598 (−0.525, 1.720)	0.283	0.665 (−0.511, 1.841)	0.256

	RCA Mean FAI		LAD Mean FAI	
Variable	**Beta Coefficient (95% Confidence Interval)**	**P value**	**Beta Coefficient (95% Confidence Interval)**	**P value**
HIV+ vs HIV+/HCV+	0.361 (−0.364, 1.085)	0.323	−0.569 (−1.321,0.184)	0.136
Age	0.008 (−0.027, 0.044)	0.651	0.019 (−0.018,0.056)	0.308
Sex	−0.390 (−1.081, 0.300)	0.262	−0.022 (−0.710,0.666)	0.949
Race	−0.494 (−1.338, 0.349)	0.245	0.396 (−0.446,1.239)	0.350
LDL-c level	−0.003 (−0.014, 0.007)	0.516	−0.003 (−0.014,0.008)	0.566
Use of lipid lowering medication	0.599 (−0.328, 1.526)	0.201	0.078 (−0.886,1.042)	0.872
BMI =>30	1.019 (0.271,1.767)	**0.008**	0.487 (−0.264,1.239)	0.199

BMI- body mass index; HCV- hepatitis C virus; HIV- human immunodeficiency virus; LAD- Left Anterior Descending artery; LDL-c- lipoprotein cholesterol; RCA- Right Coronary Artery

BMI- body mass index; HCV- hepatitis C virus; HIV- human immunodeficiency virus; LAD- Left Anterior Descending artery; LDL-c- low density lipoprotein cholesterol; RCA- Right Coronary Artery

Table 4:

Change in FAI values in Persons Living with HIV after Median of 21.8 Months[Ł]

	1st Visit (Median (Q1, Q3))	2nd Visit (Median (Q1, Q3))	P value
RCA Mean FAI (n=20)	−86.38 (−86.84, −85.61)	−85.11 (−86.00, −84.07)	0.001 *
LAD Mean FAI (n=22)	−86.55 (−86.97, −85.41)	−84.77 (−85.54, −83.82)	<0.001 *

FAI- Fat Attenuation Index; HIV- human immunodeficiency virus; LAD- Left Anterior Descending artery; RCA- Right Coronary Artery

[Ł] range of follow-up time: 20.6–27.4 months

* p value using Wilcoxon signed rank test