The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

Myocardial Steatosis Among Antiretroviral Therapy–Treated People With Human Immunodeficiency Virus Participating in the REPRIEVE Trial

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Background. People with human immunodeficiency virus (PWH) face increased risks for heart failure and adverse heart failure outcomes. Myocardial steatosis predisposes to diastolic dysfunction, a heart failure precursor. We aimed to characterize myocardial steatosis and associated potential risk factors among a subset of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) participants.

Methods. Eighty-two PWH without known heart failure successfully underwent cardiovascular magnetic resonance spectroscopy, yielding data on intramyocardial triglyceride (IMTG) content (a continuous marker for myocardial steatosis extent). Logistic regression models were applied to investigate associations between select clinical characteristics and odds of increased or markedly increased IMTG content.

Results. Median (Q1, Q3) IMTG content was 0.59% (0.28%, 1.15%). IMTG content was increased (> 0.5%) among 52% and markedly increased (> 1.5%) among 22% of participants. Parameters associated with increased IMTG content included age ($P = .013$), body mass index (BMI) ≥ 25 kg/m^2 ($P = .055$), history of intravenous drug use (IVDU) ($P = .033$), and nadir CD4 count < 350 cells/mm^3 ($P = .055$). Age and BMI ≥ 25 kg/m^2 were additionally associated with increased odds of markedly increased IMTG content ($P = .049$ and $P = .046$, respectively).

Conclusions. A substantial proportion of antiretroviral therapy–treated PWH exhibited myocardial steatosis. Age, BMI ≥ 25 kg/m^2, low nadir CD4 count, and history of IVDU emerged as possible risk factors for myocardial steatosis in this group.

Clinical Trials Registration. NCT02344290; NCT03238755.

Keywords. HIV; myocardial steatosis; intramyocardial triglyceride content; cardiovascular magnetic resonance spectroscopy; MRS; cardiometabolic risk; heart failure.

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The Journal of Infectious Diseases® 2020;222(S1):S63–9

DOI: 10.1093/infdis/jiaa245

Contemporary cohort studies demonstrate an approximately 2-fold increased risk of heart failure among people with human immunodeficiency virus (PWH) [1–5]. Of note, expanded access to antiretroviral therapy (ART) is changing the landscape of heart failure risks among PWH [6]. While unchecked human

immunodeficiency virus (HIV)/AIDS prompts overt systolic dysfunction and dilated cardiomyopathy, in ART-treated PWH, diastolic dysfunction is more commonly observed [6]. Diastolic dysfunction is an asymptomatic precursor to both heart failure with preserved ejection fraction and heart failure with reduced ejection fraction [6], and PWH evidence increased rates of both of these heart failure subtypes [4, 7, 8]. Moreover, HIV status confers increased risk for adverse outcomes among those with established heart failure [4, 8–12]. Taken together, these points underscore the need to elucidate factors contributing to heightened heart failure risks and poor heart failure outcomes among PWH.

Physiology studies exploring heart failure risk mechanisms among ART-treated PWH often focus on processes engendering diastolic dysfunction. One key pathologic process believed to induce diastolic dysfunction is myocardial steatosis, as measured by increased intramyocardial triglyceride (IMTG) content. In a healthy state, cardiomyocytes populating the myocardial structural space contain approximately 0.4%–0.5% triglycerides [13, 14]. Previous studies have shown that HIV infection confers increased risk for myocardial steatosis [15, 16] and that among PWH, the extent of myocardial steatosis relates to the degree of diastolic dysfunction [17, 18].

The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) Cardiac Dysfunction Ancillary Study leverages the REPRIEVE study [19] to explore mechanisms of myocardial pathology contributing to diastolic dysfunction among ART-treated PWH. Of note, participants in REPRIEVE were selected based on stable ART use and low-to-moderate traditional cardiovascular disease (CVD) risk [19]. This analysis presents baseline data on myocardial steatosis and associated risk factors in a subset of Ancillary Study participants who successfully completed cardiovascular magnetic resonance imaging (MRI) and cardiovascular magnetic resonance spectroscopy (MRS). Cardiovascular MRS represents the reference-standard noninvasive test for IMTG content characterization [20, 21]. Application of cardiovascular MRS in this study enables us to characterize IMTG content in a contemporary cohort of ART-treated PWH without known CVD and to explore associations between IMTG and potential demographic, behavioral, traditional metabolic, and HIV-specific risk factors.

METHODS

Recruitment of Study Participants

Individuals enrolled in REPRIEVE (ClinicalTrials.gov identifier NCT02344290) at sites near 4 participating academic centers with expertise in cardiovascular MRS (Veterans Affairs Greater Los Angeles Healthcare System [VAGLA], University of Texas Southwestern Medical Center [UTSW], Massachusetts General Hospital [MGH], and University of Cape Town Cape Universities Body Imaging Centre) were invited to co-enroll in the REPRIEVE Cardiac Dysfunction Ancillary Study (ClinicalTrials.gov identifier NCT03238755). Individuals newly enrolled in REPRIEVE were eligible for co-enrollment as long as they did not self-report a clinical diagnosis of heart failure or contraindications to cardiovascular magnetic resonance. Of the 7770 participants enrolled in REPRIEVE, 129 participants signed informed consent to co-enroll between August 2017 and February 2019. Among these, 82 successfully completed baseline cardiovascular MRS prior to the initiation of REPRIEVE study drug (at either VAGLA, UTSW, or MGH), yielding interpretable data on IMTG content.

For data elements assessed in REPRIEVE participants, see also in this supplement the article by Grinspoon et al ("Leveraging a Landmark Trial of Primary CVD Prevention in HIV"), Supplementary Methods.

Cardiovascular Magnetic Resonance Spectroscopy

Cardiovascular MRS (1H MRS) was performed at 3T magnetic field strength on MRI systems from Siemens and Philips (Siemens Skyra [VAGLA], Phillips Achieva [UTSW], and Siemens Tim Trio [MGH]), as previously described [17, 18, 22–24]. The experimental set-up for cardiovascular MRS is illustrated in Supplementary Figure 1 [25]. IMTG was quantified by a single expert reader (L. S. S.). Triglyceride content was expressed as a percentage of fat to water.

Magnetic Resonance Spectroscopy for the Assessment of Visceral Adipose Tissue

For visceral adipose tissue (VAT), a single transaxial 10-mm T1-weighted MRI slice at the level of the L2–L3 intervertebral disc with the following parameters: repetition time msec/echo time msec, 4.3/2.1; flip angle, 58°; matrix, 256 × 150; acquisition time, 14 seconds; section thickness, 10 mm. The sequence was repeated with fat saturation. Accurate manual tracing of adipose tissue was performed by a trained operator using standardized methodology.

Statistical Methods

Descriptive summaries of participant demographic, behavioral, clinical, and HIV-specific characteristics at REPRIEVE study entry (baseline) present the median (Q1, Q3) or frequency (percentage) for continuous and categorical variables, respectively. Participants were stratified into groups characterized by normal vs increased IMTG (≤ 0.5% vs > 0.5%) and normal/mildly increased vs markedly increased IMTG (≤ 1.5% vs > 1.5%) with thresholds grounded in data from relevant published studies [15, 16]. Descriptive assessments of IMTG content as related to characteristics of interest resulted in the selection of a smaller number of characteristics included in logistic regression analyses that assessed associations with increased (> 0.5%) or markedly increased (> 1.5%) IMTG content. Exploratory analyses also examined associations between IMTG and select characteristics as continuous variables; due to the skewed distribution of IMTG, Spearman rank correlations were used to

investigate these associations. Type III Wald *P* values are presented. Inference was guided by a 5% type 1 error (ie, $P < .05$). All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

Baseline Characteristics of Analysis Cohort

Baseline characteristics of the analysis cohort are presented in Supplementary Table 1.

Characteristics of Participants With Increased or Markedly Increased Intramyocardial Triglyceride Content

Median (Q1, Q3) IMTG content in the analysis cohort was 0.59% (0.28%, 1.15%), with a long-tail distribution skewed toward higher IMTG values (Supplementary Figure 2). Among the full cohort, 52% of participants had increased IMTG content (>0.5%), whereas 22% of participants had markedly increased IMTG content (>1.5%). Supplementary Table 1 presents selected characteristics of participants with IMTG values above and below these thresholds. Supplementary Table 2 presents ART exposures of participants with IMTG values above and below these thresholds.

Potential Risk Factors for Increased Intramyocardial Triglyceride Content

In logistic regression analyses, the following parameters were associated with higher odds of increased IMTG content (>0.5%): age per 5-year increase (odds ratio [OR], 1.60 [95% confidence interval {CI}, 1.10–2.33]; $P = .013$) and history of intravenous drug use (IVDU) (OR, 3.79 [95% CI, 1.12–12.87]; $P = .033$) There was also a suggestion of higher odds of increased IMTG among those with nadir CD4 count <350 cells/mm^3 (OR, 3.11 [95% CI, .98–9.90]; $P = .055$) and among those with body mass index (BMI) ≥25 kg/m^2 (OR, 2.45 [95% CI, .98–6.13]; $P = .055$). Age and BMI ≥25 kg/m^2 were associated with higher odds of markedly increased IMTG content (>1.5%) (OR, 1.58 [95% CI, 1.00–2.50], $P = .049$ for age; OR, 3.89 [95% CI, 1.02–14.76], $P = .046$ for BMI ≥25 kg/m^2). Associations of sex, race/ethnicity, waist circumference, triglyceride levels, duration of HIV, duration of ART, and current ART with increased or markedly increased IMTG content were not apparent in these analyses (Table 1).

Although there was no significant relationship between continuous VAT and odds of increased or markedly increased IMTG content, further inspection of the linearity of the ORs suggests that there may be an effect among those with the highest VAT (>75th percentile in our data). However, having VAT in the top quartile was only associated with higher odds of increased (but not markedly increased) IMTG content, and wide CIs make clear inference challenging.

Exploratory analyses performed examining IMTG as a continuous variable yielded results consistent with the primary findings, but only the relationship between age and IMTG remained statistically significant (data not shown).

DISCUSSION

Our findings highlight myocardial steatosis as a problem to be considered among ART-treated individuals with HIV and underscore potential risk factors for myocardial steatosis in this population including older age, BMI ≥25 kg/m^2, low nadir CD4 count, and self-reported history of IVDU. Our findings reinforce the importance of early detection/sustained treatment of HIV, and counseling regarding lifestyle/behavioral modification as a means of potentially mitigating myocardial steatosis.

In this cohort, median IMTG content among ART-treated PWH was 0.59%, but a sizable percentage (22%) exhibited markedly increased IMTG content (>1.5%). To our knowledge, our study represents 1 of only 4 in the field of HIV-CVD to apply cardiovascular MRS to a cohort of ≥80 PWH [15, 16, 26]. Antecedent studies of similar size reported median IMTG content ranging from 0.53% [15] to 0.79% [26] to 1.14% [16]. Important differences between our cohort and others should be noted. Participants in our study were preselected on the basis of adherence with ART, low-to-moderate traditional CVD risk, and absence of self-reported current active drug use deemed likely to compromise study participation. By comparison, in other cohorts, not all participants were ART-treated [16, 26] and select behavioral and metabolic CVD risks were more robustly represented [15, 16, 26]. Enhanced understanding of risk factors for myocardial steatosis among the global community of PWH will help clinicians identify those individuals who would benefit from closer cardiology follow-up relevant to heart failure prevention.

Our data on age and BMI as potential risk factors for myocardial steatosis among ART-treated PWH make sense in the context of previously published studies. In the general population, heart failure prevalence increases progressively across consecutive age deciles [27] and links between obesity, myocardial steatosis, and diastolic dysfunction have been described [28, 29]. Though perhaps expected, the association we observed between BMI and IMTG content among ART-treated PWH has potentially broad implications given how overweight/obesity rates have been rising in this population, particularly in relation to newly initiated ART [30].

While ART use and associated weight gain may engender myocardial steatosis, the associations between low nadir CD4 count and increased IMTG content in our data suggest a concurrent, seemingly paradoxical increase in myocardial steatosis risk conferred by deferred ART initiation. Specifically, in our study, nadir CD4 count <350 cells/mm^3 tended to be associated with increased IMTG content. Juxtaposed against previously published findings, our observations suggest that myocardial steatosis may represent a pathophysiologic intermediary between impaired immune function and heightened heart failure risks.

Table 1. Potential Risk Factors for Increased and/or Markedly Increased Intramyocardial Triglyceride Content

	IMTG Content[b]			
	IMTG > 0.5%		IMTG > 1.5%	
Characteristic[a]	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, per 5-y increase	1.60 (1.10–2.33)	.013	1.58 (1.00–2.50)	.049
Natal sex				
Male	Reference	.87	Reference	.87
Female	.89 (.24–3.36)		.88 (.17–4.54)	
Race/ethnicity				
Black non-Hispanic	.46 (.16–1.36)	.32	.83 (.25–2.77)	.73
White non-Hispanic	Reference		Reference	
Hispanic (regardless of race)	.49 (.15–1.53)		.57 (.14–2.28)	
Cocaine use				
Former	1.08 (.45–2.59)	.86	2.60 (.83–8.14)	.10
Never	Reference		Reference	
Intravenous drug use				
Former	3.79 (1.12–12.87)	.033	2.41 (.74–7.81)	.14
Never	Reference		Reference	
BMI, kg/m^2				
< 25	Reference	.055	Reference	.046
≥ 25	2.45 (.98–6.13)		3.89 (1.02–14.76)	
Waist circumference				
Normal	Reference	.31	Reference	.95
High	1.67 (.62–4.45)		.96 (.30–3.09)	
VAT, cm^2, per 75 cm^2 increase	1.40 (.88–2.24)	.16	1.15 (.68–1.94)	.61
Triglycerides, mg/dL, per 10 mg/dL increase	1.00 (.94–1.07)	.90	1.04 (.97–1.12)	.27
Nadir CD4 count, cells/mm^3				
< 350	3.11 (.98–9.90)	.055	2.61 (.54–12.68)	.23
≥ 350	Reference		Reference	
CD4 count, cells/mm^3, per 100 cells/mm^3 increase	1.07 (.94–1.21)	.33	0.97 (.83–1.14)	.72
HIV-1 RNA				
Below LLQ	Reference	.59	Reference	.21
Quantifiable	1.45 (.38–5.64)		2.43 (.60–9.81)	
Total ART use				
< 5 y	Reference	.83	Reference	.88
5–10 y	1.33 (.23–7.74)		1.71 (.16–18.73)	
> 10 y	1.59 (.33–7.76)		1.77 (.20–16.09)	
Protease exposure				
No known exposure	1.36 (.40–4.56)	.94	.83 (.18–3.86)	.58
< 5 y	Reference		Reference	
5–10 y	1.52 (.35–6.60)		2.22 (.42–11.83)	
> 10 y	1.14 (.29–4.51)		1.14 (.21–6.16)	
Thymidine exposure				
No known exposure	.96 (.27–3.39)	.50	.39 (.09–1.61)	.45
< 5 y	Reference		Reference	
5–10 y	1.00 (.20–4.95)		1.00 (.18–5.46)	
> 10 y	3.50 (.50–24.27)		.57 (.08–4.13)	
Tenofovir exposure				
No known exposure	1.83 (.28–12.07)	.45	8.00 (.57–111.96)	.25
< 5 y	Reference		Reference	
5–10 y	2.68 (.79–9.07)		7.27 (.84–62.69)	
> 10 y	2.29 (.66–8.01)		3.64 (.39–34.21)	
ART regimen class				
NRTI + INSTI	.64 (.20–1.99)	.83	.24 (.06–.98)	.25
NRTI + NNRTI	Reference		Reference	
NRTI + PI	.85 (.20–3.51)		1.11 (.26–4.82)	
NRTI-sparing	.64 (.07–5.61)		.67 (.06–7.85)	
Other NRTI-containing	.38 (.07–2.13)		.67 (.10–4.35)	

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; HIV-1, human immunodeficiency virus; IMTG, intramyocardial triglyceride; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; VAT, visceral adipose tissue.

[a]Estimates for continuous covariates are presented per clinically relevant shift in the parameter; for categorical covariates, the odds are presented relative to the specified reference category for that covariate.

[b]ORs and 95% CIs were calculated via unadjusted logistic regression. Type III Wald *P* values are presented to 2 significant figures throughout. Reported ORs (95% CIs) indicate the odds of having an increased (> 0.5%) or markedly increased (> 1.5%) IMTG content.

Specifically, in a large-scale study among PWH in the United States by Steverson et al, low nadir CD4 count was associated with a > 2-fold increased odds of adjudicated heart failure [31].

Self-reported history of IVDU emerged as a potential risk factor for myocardial steatosis among ART-treated PWH—none of whom had diabetes and very few of whom had hepatitis B or C. Indeed, in our study, self-reported history of IVDU was associated with a nearly 4-fold increased odds of IMTG content >0.5%. Previous studies in the general population have suggested a relationship between cocaine and both myocardial steatosis [32] and hepatic steatosis [33]. To our knowledge, our study is the first linking history of IVDU to increased myocardial steatosis among PWH. Of note, our study participants reporting history of IVDU did not specify whether such drug use encompassed administration of cocaine, heroin, or other agents. Moreover, we cannot rule out the possibility that links we observed between IVDU and IMTG may have been related to prior chronic hepatitis C virus. Additional work is required to elucidate whether intravenous injection of specific agents (or other risk factors more prevalent among individuals who do vs do not use intravenous drugs) underlie our observed association between IVDU and myocardial steatosis among PWH.

Our study is characterized by several limitations. To begin, due to the technical complexity of applying cardiovascular MRS, interpretable data on IMTG content was only able to be obtained on a subset of study participants. Second, due to our relatively small sample size and cross-sectional design, our determination of associations as significant should be interpreted with caution and inferences on causality/directionality of associations remain inconclusive. Finally, the extent to which findings from our study are generalizable to the broader global community of PWH remains unclear.

Our findings build on previously published findings among PWH showing a close association between myocardial steatosis and diastolic dysfunction [17, 18], as well as increased heart failure risks or worse heart failure outcomes [4, 8–12]. Our observation of low nadir CD4 count as a potential risk factor for myocardial steatosis reinforces the importance of early detection and treatment of HIV. Furthermore, our observation that BMI ≥ 25 kg/m^2 and IVDU may represent risk factors for myocardial steatosis highlights potential benefits of clinic-based counseling on healthy lifestyle. As technical complexity may limit application of cardiovascular MRS in clinical practice, investigations employing this technology will be required to more carefully elucidate the etiopathology of myocardial steatosis among PWH. Such investigations will facilitate the development and delivery of targeted heart failure prevention efforts among ART-treated PWH (Supplementary Figure 3).

Supplementary Data

Supplementary materials are available at *The Journal of 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

Acknowledgments. The study investigators thank the study participants, site staff, and study-associated personnel for their ongoing participation in the trial. Additionally, we thank the AIDS Clinical Trial Group (ACTG) for clinical site support; the ACTG Clinical Trials Specialists for regulatory support; the data management center at Frontier Science Foundation for data support; and the Center for Biostatistics in AIDS Research for statistical support.

Disclaimer. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institutes of Health (NIH), or the US Department of Health and Human Services.

Financial support. This work was supported by the NHLBI (grant numbers U01 HL123336, U01 HL123339 and R01HL137562), with additional support from the NIAID (UM1 AI068636 and UM1 AI106701).

Supplement sponsorship. This supplement is sponsored by Massachusetts General Hospital, through NIH funding including U01HL123336.

Potential conflicts of interest. T. G. N. reports personal fees from Aprea Therapeutics, H3 Biomedicine, BMS, Intrinsic Imaging, and Parexel, outside the submitted work. K. W. C. reports grants from NIH/NIAID, during the conduct of the study, and a clinical trial contract with Amgen, outside the submitted work. L. M. reports grants from NIH/NHLBI during the conduct of the study, as well as grants from NIH/NIAID, outside the submitted work. T. H. B. reports financial support from Excision BioTherapeutics (equity less than $10 000), outside the submitted work. P. E. S. reports grants from NIH during the conduct of the study; and grants from Gilead Sciences and personal fees from Gilead Sciences, Merck and Company, Janssen, and ViiV Healthcare, outside the submitted work. D. J. S. reports grants from Massachusetts General Hospital during the conduct of the study. R. J. L. reports personal fees and nonfinancial support from Gilead Sciences, Merck and Company, and Roche, outside the submitted work. E. D. reports grants from NIH during the conduct of the study; and grants from Gilead Sciences, ViiV Healthcare, and Merck and Company and personal fees from Theratechnologies, Gilead Sciences, and ViiV Healthcare, outside the submitted work. G. K. R. reports grants from Citius Pharmaceuticals, Emergent Biosolutions, Gilead Sciences, Pfizer, and Leonard Meron Biosciences, outside the submitted work. K. V. F. reports an educational grant from Gilead Sciences, outside the submitted work. J. S. C. reports personal fees from Merck and Company, outside the

submitted work. P. S. D. reports grant support from Kowa Pharmaceuticals America and Gilead Sciences, for the conduct of the study. U. H. reports grants from NIH/NHLBI and from Kowa Pharmaceuticals America, during the conduct of the study; and grants from Duke University (Abbott), HeartFlow, and MedImmune/AstraZeneca and personal fees from Duke University (NIH) and ReCor Medical, outside the submitted work. S. K. G. reports grant support through his institution from Kowa Pharmaceuticals America and Gilead Sciences, for the conduct of the study; and grants from Theratechnologies, Navidea, and ViiV Healthcare, outside the submitted work. H. J. R. reports grants from NIH/NHLBI during the conduct of the study; and grants from Kowa Pharmaceuticals America, outside the submitted work. M. K. J. reports grants from Janssen, Merck and Company, GSK/ViiV, and VasGene, and grants and personal fees from Gilead Sciences, outside the submitted work. A. W. reports grants from NIH during the conduct of the study. M. V. Z. reports an investigator-initiated research grant from Gilead Sciences to her institution, outside the submitted work. All other authors report no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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