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Cocaine use may modify HIV/ART-associated myocardial steatosis and hepatic steatosis

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Abstract

Background—It has been recognized that myocardial and hepatic steatosis may be more prevalent in HIV-infected individuals on antiretroviral therapy (ART); however, factors associated with these conditions have not been thoroughly investigated. The goals of this study were (1) to identify the risk factors for myocardial and hepatic steatosis in HIV-infected African Americans (AAs) and explore whether ART use is independently associated with myocardial and hepatic steatosis, and (2) to examine whether and how cocaine use influences any associations of ART use with myocardial and hepatic steatosis.

Methods—Between June 2010 and December 2013, 220 HIV-infected AAs in Baltimore, Maryland, were enrolled in a study investigating HIV/ART-associated myocardial and hepatic damage. Proton magnetic resonance spectroscopy was performed to quantify myocardial and hepatic triglyceride contents. Sociodemographic, medical and laboratory data were also obtained. Robust regression model was employed to perform primary statistical analysis.

Results—Robust regression analyses showed that (1) duration of protease inhibitor (PI) use was independently associated with myocardial and hepatic triglyceride contents, (2) duration of PI use was independently associated with myocardial triglyceride in cocaine users ($p = 0.025$), but not in

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Contributors

Drs. Lai S, Gerstenblith, Li, and Lai H designed the study and conducted the analyses and prepared a draft of the manuscript. Dr. Lai H undertook the statistical analyses. All 11 authors contributed to, and have approved the final manuscript.

Conflict of interest

No conflict of interest declared.

cocaine never-users ($p = 0.84$), and (3) duration of PI use was independently associated with hepatic triglyceride in cocaine users, but not in cocaine never-users ($p = 0.52$).

Conclusions—Cocaine use may trigger/exacerbate the toxicity of PI in ART-associated myocardial and hepatic steatosis, suggesting that cocaine abstinence/reduced use may retard these ART-associated comorbidities. Clinical trials should be conducted to examine whether reduced cocaine use improves HIV/AIDS-associated myocardial and hepatic steatosis.

Keywords

Myocardial triglyceride content; Hepatic triglyceride content; African Americans; Antiretroviral therapy; Cocaine use; HIV infection

1. Introduction

Free fatty acids are well recognized as the major source of energy for the myocardium. Under normal conditions, the majority of free fatty acids in the myocardium undergo rapid oxidation and little is stored. But when fatty acids influx into myocardial cells exceeds the oxidative needs, the excess fatty acids may be stored as triglycerides, resulting in myocardial, or cardiac, steatosis (Schaffer, 2016). As a new marker for LV dysfunction, myocardial steatosis is common in patients with diabetes or obesity, and is associated with lipopoptosis (Szczepaniak et al., 2003; Reingold et al., 2005; McGavock et al., 2006; McGavock et al., 2007; Szczepaniak et al., 2007; Rijzewijk et al., 2008). Animal model studies suggest that myocardial steatosis may result in cardiac dysfunction and eventual cardiomyopathy (Glenn et al., 2011; Zhou et al., 2000). However, the mechanisms responsible for the development of myocardial steatosis and the factors associated with myocardial steatosis in humans are not fully understood. In addition to its association with metabolic syndrome and diabetes, antiretroviral therapy (ART) used in treating HIV infection may also be associated with myocardial steatosis in persons with HIV infection (Holloway et al., 2013; Nelson et al., 2014; Thiara et al., 2015; Lai, 2013). Nevertheless, the risk factors for myocardial steatosis in those with HIV infection have not yet been thoroughly investigated. Also, since cocaine use is known to modify the association between body mass index and myocardial steatosis (Lai et al., 2015), it is important to examine whether cocaine use is an effect modifier in the association of ART use with myocardial steatosis in HIV-infected persons.

In addition to myocardial steatosis, ART may also be associated with hepatic steatosis, a condition that may lead to liver inflammation (Moreno-Torres et al., 2007; Hadigan et al., 2007).

This investigation had four objectives. The first was to examine whether ART use is independently associated with myocardial steatosis, the second to assess whether and how cocaine use influences any association between ART use and myocardial steatosis, the third to examine whether ART use is independently associated with hepatic steatosis, and the fourth to assess whether and how cocaine use influences any association between ART use and hepatic steatosis. The data were derived from an ongoing longitudinal study examining

the cardiovascular complications of HIV infection and chronic cocaine use in an African American (AA) population in Baltimore, Maryland, USA.

2. Methods

2.1. Participants

Between June 2010 and December 2013, 436 African American (AA) men and women with and without HIV infection, and with/without chronic cocaine use in Baltimore, Maryland, were consecutively enrolled in a prospective study investigating the effects of HIV infection, prolonged ART exposure and chronic cocaine use on myocardial steatosis, defined by the accumulation of triglyceride in heart tissues as detected by cardiac magnetic resonance spectroscopy (MRS). The HIV-infected AAs were recruited from the Johns Hopkins Adult HIV clinic. The HIV-uninfected AAs were recruited from the eastern part of Baltimore City, where the majority of HIV-infected participants reside. Of these 436, 220 were HIV-infected.

Inclusion criteria were (1) age $\geq$ 21 years; (2) HIV positivity, as determined by ELISA and confirmed by Western blot test; (3) cocaine use: defined as use by any route for at least 6 months, administered at least 4 times/month. Infrequent users (fewer than 4 times/month, or <6 consecutive months) were not recruited. Chronic cocaine users who also used other drugs such as opiates or alcohol were included. Non-cocaine use was defined as never having used cocaine or not having used in the past 5 years or longer; assessment of cocaine use was based on self-reported use; and (4) AA race (self-designated). Exclusion criteria were (1) any evidence of clinical coronary artery disease (CAD) or any history of or current symptoms or diagnoses related to cardiovascular disease; (2) pregnancy; and (3) history of MRI-related claustrophobia.

The Johns Hopkins School of Medicine Institutional Review Board approved the study protocol and consent form (IRB ID number, NA_00049784), and all study participants provided written informed consent. All procedures used in this study were in accordance with institutional guidelines. Although the overall investigation is a cohort study, the data presented herein are cross-sectional (baseline) only.

2.2. Main procedures

2.2.1. Interview, medical chart review, physical and laboratory examination—

During the baseline visit, study participants underwent a detailed interview to obtain information about sociodemographic characteristics, medical history, behaviors, including alcohol consumption, drug use, and cigarette smoking, and medications. For HIV-infected participants, detailed information about HIV-related risk factors, duration of known HIV infection, and medications, including ART use, was also collected. A medical chart review was used to confirm the information on medical history and medications provided by the study participants. A physical examination was performed and vital signs were recorded. Routine clinical laboratory blood chemistry tests were conducted. The following laboratory tests were performed at baseline: total serum cholesterol, triglycerides, high-density

lipoprotein (HDL), low-density lipoprotein (LDL), glucose, and inflammation markers, including high-sensitivity C-reactive protein (hsCRP).

2.2.2. Myocardial and hepatic imaging and spectroscopy—All studies were performed on a 3.0-T MR scanner (Trio Tim; Siemens, Erlangen, Germany) with a six-channel phased-array torso coil and combined with posterior coil elements resulting in 12 channels of data. Participants were instructed to hold their breath at end expiration during imaging and to breathe normally during spectroscopy. To measure left ventricular (LV) function, the heart was imaged in both long and short-axis orientations, using retrospectively gated steady state free precession cine images. One grid tagged short-axis slice was obtained at the middle LV.

Myocardial ^1H MRS spectra were obtained with electrocardiogram gating during early systole, with navigator gating to enable free-breathing using a single voxel point-resolved spectroscopy sequence. The spectroscopic volume (6- to 8-mL voxel) was positioned within the interventricular septum. The navigator was placed across the liver-lung interface. For reliable measurement of the low-fat signals, one spectrum was recorded with water suppression (32 averages), and another spectrum (eight averages) was recorded without water suppression (Venkatesh et al., 2012).

Measurement of hepatic triglyceride content was performed using the same sequence with the MRS voxel placed in the right hepatic lobe. Eight averages of water suppressed as well as eight averages of no water suppressed spectrum were acquired with breath holding.

2.2.3. MRI data analysis—Java-based MR software (jMRUI v.3.0 software; A. van den Boogaart, Katholieke Universiteit Leuven, Leuven, Belgium) was used to process spectral data, and the reader was blinded to the participants' characteristics (Naressi et al., 2001). The areas under the resonance frequency estimates of lipids at 0.9 and 1.3 ppm were summed to quantify myocardial triglyceride content and related to water in unsuppressed spectra. Myocardial fat fraction was expressed as the ratio of fat to water and reported as a percentage, while hepatic fat fraction was expressed as the ratio of fat to water plus fat and also reported as a percentage.

2.3. Statistical analysis

2.3.1. Pre-study calculation of the required sample size—Pre-study sample size was calculated to test a hypothesis that ART use and cocaine use have a synergistic effect. According to the results of previous regression analyses, the R^2 for cocaine use and the R^2 for ART use were roughly identical (0.10). It was assumed that the smallest effect of ART or cocaine that would be important to detect was an increment of 6% (to the R^2). The alpha was set to 0.01 and the test was two-sided. It was further assumed that 6% of the variance was explained by the interaction between ART and cocaine use. The sample size/power estimation was based on (Cohen, 1988a, 1988b). With a sample size of 160, the power to test the above-mentioned hypothesis would be 0.82. It was assumed that the dropout rate would be 5% per year. With 200 at baseline, 160 participants would remain in the study after adjusting for the dropouts. Therefore, with a sample size of 200, the power to test this hypothesis would be 0.82. Due to a high prevalence of MRI claustrophobia in the study

population, we actually recruited 10% more participants than planned (the actual sample size for HIV-infected was 220).

2.3.2. Data analysis—Statistical analysis was performed with SAS (SAS 9.4, SAS Institute, Cary, NC). All continuous parameters were summarized by medians with interquartile ranges (IQRs), and all categorical parameters were summarized as proportions. To compare between-group differences in demographic and clinical characteristics, lipid profiles, and other factors, non-parametric ANOVA was used for continuous variables and the Chi-square test was employed for categorical variables.

The data for this investigation included sociodemographic characteristics, medical history, behaviors, including alcohol consumption, drug use, cigarette smoking, medications, laboratory and imaging parameters, some of which may not be normally distributed and inevitably contain “outliers”. Since outliers can be masked and very hard to detect in multivariate or highly structured settings, and since conventional multiple linear regression models, based on ordinary least squares, could yield misleading results if assumption of the normal distribution is not true, robust regression model with the least trimmed squares (LTS) estimation method was used to provide robust results in the presence of outliers (Rousseeuw and Leroy, 1987). Robust regression fits a linear regression model that is robust in the presence of outliers or high leverage points (with “extreme” or outlying values of the independent variables). Univariate robust regression models were first fitted to evaluate the crude associations between myocardial and hepatic triglyceride contents and each individual factor, including age, sex, years of cigarette smoking, number of cigarettes smoked per day, years of alcohol consumption, number of alcohol drinks consumed per week, heavy drinking (defined as >14 drinks per week for men, and >7 drinks per week for women), years of cocaine use, times of cocaine used per day, HCV infection, hypertension, diabetes, high-sensitivity C-reactive protein, systolic blood pressure, diastolic blood pressure, fasting glucose, BMI, total cholesterol, high density lipoprotein cholesterol, triglycerides, ACC/AHA cardiovascular risk score according to the 2013 American College of Cardiology/American Heart Association guidelines (Goff et al., 2014), years since HIV infection was diagnosed, the nadir CD4 cell count (defined as the lowest CD4 cell count after HIV infection was diagnosed), CD4 cell count when MRS was performed, HIV viral load level (log-transformed) when MRS was performed, months of NRTI (nucleoside reverse transcriptase inhibitors) use, months of NNRTI (non-nucleoside reverse transcriptase inhibitors) use, and months of PI (protease inhibitors) use. Those factors that were significant at the $P < 0.15$ level in the univariate models were put into the multivariate robust regression models to investigate the joint effect of these factors on myocardial and hepatic triglyceride contents. In order to examine whether duration of each class of ART was independently associated with myocardial and hepatic triglyceride contents, the importance of each variable included in the multivariate model was evaluated with 1) an examination of the Wald statistic for each variable in the model and 2) a comparison of each estimated regression coefficient in the multivariate model with the regression coefficient from the corresponding univariate model. Those variables that ceased to make significant contributions to the models based on these two criteria were deleted in a stage wise manner, and a new model was refitted. This process of eliminating, refitting, and verifying continued

until all of the variables included were statistically significant, yielding a final model. The P-values reported are two-sided, and $P < 0.05$ indicates statistical significance.

3. Results

3.1. General characteristics

General characteristics of the study participants by cocaine use status are presented in Table 1. Of the 220 participants in this study, 55 (25.0%) were chronic cocaine users. Their median age was 47 (IQR: 42–51) years, and 127 (57.7%) were males. According to the 2013 ACC/AHA cardiovascular risk score algorithm (Goff et al., 2014), 148 (67.3%) of the study participants had a low risk of CAD. The median BMI was 26 (23–30) kg/m^2 . The median myocardial triglyceride content was 0.79 (IQR: 0.42–1.44) and the median hepatic triglyceride content was 1.87 (IQR: 0.88–4.75).

There were significant differences in cigarette smoking ($P < 0.0001$), duration of cigarette smoking ($P < 0.0001$), alcohol consumption ($P = 0.02$), duration of alcohol consumption ($P = 0.002$), and total cholesterol ($P = 0.02$), between cocaine users and nonusers.

3.2. Association between duration of ART use and myocardial triglyceride content

The multivariate robust regression analysis results presented in Table 2 show that BMI ($P = 0.009$) and duration of PI use ($P = 0.002$) were significantly associated with myocardial triglyceride content. The final model showed that only BMI (regression coefficient: 0.0243, SE: 0.0069, $P = 0.0004$) and duration of PI use (regression coefficient: 0.0026, SE: 0.0007, $P = 0.0002$) were independently associated with myocardial triglyceride content.

3.3. Cocaine use modified the association between duration of ART use and myocardial triglyceride content

Per the multivariate robust regression analysis results presented shown in Table 3, duration of PI use was not significantly associated with myocardial triglyceride content ($P = 0.84$) in those who had never used cocaine. The final model for cocaine never users showed that only BMI (regression coefficient: 0.0324, SE: 0.0095, $P = 0.0006$) and HDL (regression coefficient: 0.0106, SE: 0.0035, $P = 0.003$) were independently associated with myocardial triglyceride content.

However, multivariate analysis showed that duration of PI use was significantly associated with myocardial triglyceride content ($P = 0.049$) in those who used cocaine (Table 3). The final model for cocaine users showed that male sex (regression coefficient: -0.2106 , SE: 0.1010, $P = 0.0037$) and duration of PI use (regression coefficient: 0.0024, SE: 0.0011, $P = 0.026$) were independently associated with myocardial triglyceride content.

3.4. Association between duration of ART use and hepatic triglyceride content

The results of the multivariate robust regression analysis presented in Table 4 show that only BMI ($P < 0.0001$) was significantly associated with hepatic triglyceride content. The final model showed that BMI (regression coefficient: 0.0847, SE: 0.0178, $P < 0.0001$) and

duration of PI use (regression coefficient: 0.0037, SE: 0.0018, $P = 0.042$) were independently associated with hepatic triglyceride content.

3.5. Cocaine use modified the association between duration of ART use and hepatic triglyceride content

Per the results of the multivariate robust regression analysis presented in Table 5, duration of PI use was not significantly associated with myocardial triglyceride content ($P = 0.52$) in those who had never used cocaine. The final model for cocaine never users showed that only BMI (regression coefficient: 0.0589, SE: 0.0261, $P = 0.024$) was independently associated with hepatic triglyceride content.

Multivariate robust regression analysis showed that the duration of PI use was not significantly associated with hepatic triglyceride content ($P = 0.049$) in those who used cocaine (Table 5). However, the final model for cocaine users showed that BMI (regression coefficient: 0.0818, SE: 0.0236, $P = 0.0005$) and duration of PI use (regression coefficient: 0.0074, SE: 0.0030, $P = 0.014$) were independently associated with hepatic triglyceride content.

3.6. Associations between individual PI and myocardial/hepatic triglyceride content

The effect of individual PI used by study participants on myocardial and hepatic triglyceride contents was examined by robust regression analyses. Since these PIs predominantly affect cocaine users, our analyses were performed in cocaine users only. Among the PIs examined, including amprenavir, tipranavir, indinavir, lopinavir/ritonavir, fosamrenavir, ritonavir, darunavir, atazanavir, saquinavir, nelfinavir, brexanavir, and lopinavir, duration of tipranavir use was independently associated with myocardial triglyceride content after adjusting for male sex (regression coefficient with SE: 1.0686 with S.E: 0.1964, P -value: < 0.0001), while duration of darunavir use (regression coefficient with SE: 0.0240 with S.E: 0.0120, P -value: 0.045), duration of ritonavir use (regression coefficient with SE: 0.0101 with S.E: 0.0047, P -value: 0.032), and duration of indinavir/ritonavir use (regression coefficient with SE: 0.0849 with S.E: 0.0180, P -value: < 0.0001) were independently associated with hepatic triglyceride content after adjusting for cholesterol levels.

3.7. Associations between alcohol consumption and myocardial/hepatic triglyceride content

According to robust regression analyses, no significant associations between alcohol use (duration of alcohol use, alcohol drinks per week or heavy drinking) and myocardial/hepatic triglyceride were identified (Tables 2–5).

3.8. Associations between HCV infection and myocardial/hepatic triglyceride content

According to robust regression analyses, the presence of HCV infection was independently associated with hepatic triglyceride content (Table 4).

4. Discussion

4.1. Major findings

In this study, we found that (1) duration of PI use was independently associated with both myocardial and hepatic steatosis, (2) chronic cocaine use modified the association of duration of PI use with both myocardial and hepatic triglyceride content.

4.2. Factors associated with myocardial triglyceride

We found that among the factors investigated, BMI and duration of PI use were independently associated with myocardial triglyceride content. Cumulative evidence indicates that obesity is not only an established risk factor for type-2 diabetes and coronary artery disease, but also leads to the over-accumulation of lipids in non-adipose tissues, including the heart (Schaffer 2016; Szczepaniak et al., 2003; Reingold et al., 2005; McGavock et al., 2006; McGavock et al., 2007; Szczepaniak et al., 2007; Rijzewijk et al., 2008; Kusminski et al., 2009). Our findings support previous studies that suggested that obesity plays a critical role in myocardial steatosis.

Our study suggested that duration of PI use was independently associated with myocardial steatosis, which has not been reported before. Animal studies have demonstrated that myocardial triglyceride content in rats exposed to PI (lopinavir/ritonavir) was significantly elevated compared to those who received placebo (Reyskens et al., 2013). It is known that some of the PIs elevate blood triglyceride levels, probably due to increased hepatic synthesis of triglycerides, however, our study suggested that elevated blood triglyceride levels were not independently associated with myocardial steatosis, although some of these patients may have been on a statin or other medications that would decrease triglyceride levels. Our study did not find significant associations of HIV-related factors or conventional cardiovascular risk factors with myocardial triglyceride content. Further studies are needed to confirm our findings.

The exact mechanisms by which myocardial steatosis develops are not fully understood and the mechanism of action of cocaine on the effect of the association between duration of PI use and myocardial steatosis remains unexplained. A hypothetical mechanism for cocaine as an effect modifier is that cocaine is a potent stimulant of the sympathetic nervous system, and the sympathetic effects of cocaine may inhibit the leptin system, leading to less leptin production (Trayhurn et al., 1998; Vongpatanasin et al., 1999; Rayner and Trayhurn, 2001; Ersche et al., 2013; Manetti et al., 2014). Leptin has been recognized as an antisteatotic hormone, preventing the deleterious consequences of ectopic fatty acids overload in nonadipose tissue, such as the myocardium (Trayhurn et al., 1998; Trayhurn et al., 1999; Rayner et al., 2001; Unger, 2002).

4.3. Cocaine use modified the associations of duration of PI use with myocardial triglyceride content

This study showed that the effect of duration of PI use on myocardial triglyceride content may depend on cocaine use status: in those who had never used cocaine, the association between duration of PI use and myocardial triglyceride content was not significant ($P = 0.84$,

Table 3), while in chronic cocaine users, duration of PI use was independently associated with myocardial triglyceride content, even after controlling for potential confounding factors ($P = 0.026$). We previously reported that cocaine use may modify the association between obesity measures and myocardial triglyceride content (Lai et al., 2015); this study suggested that cocaine use may have triggered and/or exacerbated the cardiotoxicity of PI, which has not been reported before. The potential interaction between cocaine use and PI toxicity has also not been thoroughly investigated.

4.4. Factors associated with hepatic triglyceride

We found that BMI and duration of PI use were independently associated with hepatic triglyceride content. Obesity is linked to the over-accumulation of lipids in non-adipose tissues, including the liver (Schaffer 2016; Szczepaniak et al., 2003; Reingold et al., 2005; McGavock et al., 2006; McGavock et al., 2007; Szczepaniak et al., 2007; Rijzewijk et al., 2008; Kusminski et al., 2009).

Our study suggested that the duration of PI use is independently associated with hepatic steatosis, which has never been reported before. Animal studies demonstrated that hepatic triglyceride content in rats that were exposed to PI (lopinavir/ritonavir) was significantly elevated compared to those exposed to placebo (Reyskens et al., 2013). It is known that some of the PIs elevate blood triglyceride levels, probably due to increased hepatic synthesis of triglycerides; however, our results indicate that elevated blood triglyceride levels are not independently associated with hepatic steatosis. The exact mechanisms by which hepatic steatosis develops in HIV-infected persons on PI are not fully understood. Hepatic steatosis may lead to liver inflammation and chronic liver inflammation result in hepatic fibrosis (Moreno-Torres et al., 2007; Hadigan et al., 2007; Czaja, 2004; Wicklow et al., 2012). Our study did not find significant associations of HIV-related factors or conventional cardiovascular risk factors with hepatic triglyceride content. Further studies are needed to confirm our findings.

Our study also suggested that among all the PIs, including amprenavir, tipranavir, indinavir, lopinavir/ritonavir, fosamrenavir, ritonavir, darunavir, atazanavir, saquinavir, nelfinavir, brexanavir, and lopinavir, duration of tipranavir use was independently associated with myocardial triglyceride content after adjusting for male sex, while duration of darunavir use, duration of ritonavir use, and duration of indinavir/ritonavir use were independently associated with hepatic triglyceride content after adjusting for cholesterol levels. The effect of tipranavir use on myocardial triglyceride has not been reported. Despite being well tolerated, clinical hepatitis and hepatic decompensation, and intracranial hemorrhage have been associated with tipranavir (Orman and Perry, 2008). Although liver enzyme elevation during darunavir-based antiretroviral treatment in HIV-1-infected patients with or without hepatitis C coinfection was reported (Di Biagio et al., 2014), the effects of darunavir, on hepatic triglyceride also have not been reported. The use of ritonavir has been frequently implicated in hypertriglyceridemia and lipodystrophy, though the effect of ritonavir on hepatic steatosis has not been reported. Indinavir/ritonavir-associated renal toxicity has been reported, however, the effect of indinavir/ritonavir was also not investigated (Cressey et al., 2007). Large longitudinal studies are needed to confirm these findings.

4.5. Cocaine use modified the associations of duration of PI use with hepatic triglyceride content

This results of this study indicate that the effect of duration of PI use on hepatic triglyceride content depends on cocaine use status: in those who had never used cocaine, the association between duration of PI use and hepatic triglyceride content was not significant ($P = 0.52$, Table 5), while in chronic cocaine users, duration of PI use was significantly associated with hepatic triglyceride content even was independently associated with hepatic triglyceride content ($P = 0.014$).

The mechanisms responsible for how cocaine use modifies the relationships between duration of PI use and hepatic steatosis are unknown and further investigations are needed.

4.6. Cocaine may exacerbate the toxic effects of ART

The most provocative finding derived of this investigation is that chronic cocaine use may trigger/exacerbate the toxicity of PIs in HIV/ART-associated myocardial and hepatic steatosis. We recently reported that long-term (> 36 months, 36 was the median of ART use duration) use of ART was independently associated with a higher risk of subclinical atherosclerosis in cardiovascularly asymptomatic African Americans with HIV infection, and that cocaine use may trigger and/or exacerbate subclinical atherosclerosis in those who had used ART for longer than 36 months (Lai et al., 2016): multivariate Poisson regression analyses showed that compared to those who were ART naïve, those who had never used cocaine and had used ART ≥ 36 months were not at significantly higher risk for any CT outcome variables, whereas chronic cocaine users who had used ART for ≥ 36 months were at significantly higher risk for the presence of coronary stenosis (the propensity score-adjusted PR, 1.87; 95% CI, 1.19, 2.94; P -value, 0.007), noncalcified plaque (the propensity score-adjusted PR, 2.46; 95% CI, 1.30, 4.66; P -value, 0.006), and subclinical CAD (the propensity score-adjusted PR, 1.62; 95% CI, 1.17, 2.35; P -value, 0.011). Taken together, these findings strongly suggest that (1) although ART substantially reduces HIV/AIDS-related mortality, long-term exposure to ART may be associated with subclinical atherosclerosis, as well as myocardial and hepatic steatosis leading to organ dysfunction, and (2) these ART-associated comorbidities could potentially be reduced or minimized in cocaine users with HIV infection if cocaine dependence could be treated. Cocaine is highly addictive and cocaine use is still prevalent in those with HIV-infection. Thus, further studies on whether reduced cocaine use leads to reduced HIV/ART-associated comorbidities must be a high priority for managing HIV disease and preventing HIV/ART-associated subclinical and clinical comorbidities in HIV-infected AAs.

4.7. Limitations

There are some potential major limitations of this study which merit discussion. First, because all the study participants were AAs, the results derived from this investigation may not be generalized to other race/ethnic groups without caution. Further studies may be warranted to examine the racial/ethnic differences in the effect of cocaine use on myocardial/hepatic steatosis. We recognize that the cardiac, metabolic and other disease burdens are high among AAs; nevertheless, we have not conducted similar studies in other populations. Second, since a cross-sectional study could not examine changes in alcohol

consumption in relation to myocardial/hepatic steatosis, this investigation may have failed to identify the effect of alcohol use on cardiac and hepatic steatosis. Likewise, we may have also failed to identify the effect of cocaine use on cardiac and hepatic steatosis based on changes since that use. Third, due to the nature of the cross-sectional design, some hidden confounding factors, such as socioeconomic status, were not adjusted for. Fourth, the study sample may not be representative of the population from which it was selected.

5. Conclusions

This study suggests that duration of PI use is associated with increased myocardial and hepatic triglyceride contents, although larger longitudinal studies are needed to confirm this finding.

This results of this study also indicate that cocaine use could exacerbate ART-induced toxicity in HIV-infected cocaine users. We believe that these findings are sufficient to alert physicians and other health care providers to inform their patients with HIV infection of the dangers of cocaine use and, specifically, that it is associated with myocardial and hepatic steatosis, and the likely consequent organ dysfunction.

In a statement on NIH efforts to focus research to end the AIDS epidemic, Dr. Collins has declared that improving the prevention and treatment of HIV-associated comorbidities is one of the NIH high-priority areas of HIV/AIDS research (Collins, 2015). Since cocaine use is prevalent in the U.S., especially in AAs with HIV infection, and significant steatosis likely leads to myocardial and hepatic dysfunction, and since abstinence from cocaine use or even reduced cocaine use can be achieved in AAs with HIV infection (Lai et al., 2015), a randomized clinical trial should be conducted to confirm whether reduced cocaine use improves HIV/AIDS-associated myocardial and hepatic steatosis.

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Table 1

Characteristics of study participants in Baltimore, Maryland.

Characteristic	All (N = 220)	Never use of cocaine (N = 55)	Chronic use of cocaine (N = 165)	p-value
Age (year)	47 (42–51)	46(35–51)	47 (43–51)	0.09
Male sex	57.7	61.8	56.4	0.48
Cigarette smoking (%)	82.7	56.4	91.5	< 0.0001
Years of cigarette smoking	22 (6–32)	2 (0–23)	25 (16–34)	< 0.0001
Number of cigarettes smoked/day	5 (2–10)	1.5 (0–5)	6 (3–10)	< 0.0001
Alcohol use (%)	90.0	81.8	92.7	0.02
Years of alcohol use	19 (5–30)	10 (1–20)	20 (10–30)	0.002
Number of alcohol drinks/week	4 (2–10)	2 (1–5)	2 (2–22)	0.0002
Heavy drinking (%)	20.9	7.3	25.5	0.004
Chronic cocaine use (%)	75.0	0.0	100.0	< 0.0001
Years of cocaine use	10 (1–19)	0 (0–0)	15 (8–20)	< 0.0001
Times of cocaine use/day	2 (0–5)	0 (0–0)	3 (2–5)	< 0.0001
Hypertension (%)	15.5	16.4	15.2	0.83
Diabetes (%)	3.2	0.0	4.3	0.20
BMI (kg/m ²)	26 (23–30)	25 (22–28)	26 (23–31)	0.56
hsCRP 2 mg/dL (%)	42.9	45.5	42.1	0.66
hsCRP (mg/dL)	1.6 (0.5–3.9)	1.8 (0.6–4.9)	1.5 (0.5–3.7)	0.13
Systolic BP (mm Hg)	119 (110–129)	119 (111–130)	119 (110–128)	0.70
Diastolic BP (mm Hg)	75 (67–82)	73 (64–84)	75 (68–81)	0.33
Glucose (mg/dL)	84 (77–94)	85 (77–92)	84 (77–94)	0.59
Total cholesterol (mg/dL)	165 (135–195)	180 (141–200)	161 (135–191)	0.02
LDL-C (mg/dL)	80 (63–1108)	95 (69–123)	79 (61–101)	0.16
HDL-C (mg/dL)	51 (40–65)	49 (42–60)	52 (39–67)	0.50
Triglycerides (mg/dL)	104 (77–153)	103 (72–147)	105 (79–154)	0.10
2013 ACC/AHA risk (%)	5.3 (17–8.9)	3.6 (0.9–8.2)	5.9 (1.9–9.1)	0.12
HCV infection (%)	45.0	14.8	54.9	< 0.0001
Years since HIV was diagnosed	12(7–18)	10(4–20)	13(9–18)	0.32
CD4 count nadir (cells/mm ³)	199(70–351)	291(68–414)	195(71–286)	0.25

Characteristic	All (N = 220)	Never use of cocaine (N = 55)	Chronic use of cocaine (N = 165)	p-value
CD4 count at MRS (cells/mm ³)	479(308–679)	432(319–616)	481(308–679)	0.91
HIV RNA at MRS (copies/mL)	400(22–24702)	37(20–400)	48(20–781)	0.82
ART use (%)	76.8	72.7	78.2	0.41
NRTI use (%)	69.1	63.6	70.9	0.31
NNRTI use (%)	34.1	32.7	34.6	0.80
PI use (%)	57.7	47.3	61.2	0.06
Months of ART use	30.5(0.9–87.0)	21(0.0–96.0)	36.0(2.0–86.0)	0.52
Months of NRTI use	16.9(0.0–60.0)	12(0.0–53.0)	24.0(0.0–67.0)	0.31
Months of NNRTI use	0.0(0.0–12.0)	0.0(0.0–12.0)	0.0(0.0–12.0)	0.67
Months of PI use	5.5(0.0–48.0)	0.0(0.0–48.0)	6.0(0.0–48.0)	0.38
Myocardial triglyceride content(%)	0.79 (0.42–1.44)	0.65 (0.40–1.31)	0.87 (0.44–1.72)	0.67
Hepatic triglyceride content (%)	1.87(0.88–4.75)	1.39(0.67–3.80)	2.14(1.07–4.87)	0.056

* Median (interquartile range) for continuous variables, proportion (%) for categorical variables.

Abbreviations: hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; glucose, fasting glucose; BMI, body mass index (kg/m²); LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; 2013 ACC/AHA risk, cardiovascular risk score based on 2013 American College of Cardiology/American Heart Association (ACC/AHA) cardiovascular risk calculator (Goff et al., 2014); HCV infection, persons who were positive for HCV antibodies by 2 enzyme immunoassay were considered to be HCV antibody positive and are hereafter referred to as HCV infected.

CD4 count nadir, the lowest CD4 count since HIV diagnosis; CD4 count at MRS, the CD4 count when magnetic MR spectroscopy was performed; HIV RNA at MRS, the HIV viral load when magnetic MR spectroscopy was performed; ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

Table 2

Associations of demographic, laboratory, and clinical factors with myocardial triglyceride in all study participants, robust regression analysis.

Variable	Univariate model		Final multivariate model	
	regression estimate(SE)	p-value	regression estimate(SE)	p-value
Age (year)	-0.0000(0.0058)	0.99		
Male sex	-0.2098(0.0886)	0.018		
Years of cigarette smoking	-0.0002(0.0032)	0.94		
Number of cigarettes smoked/day				
3	reference			
> 3 but ≤ 10	-0.1669(0.0929)	0.07		
> 10	-0.0765(0.1268)	0.54		
Years of alcohol use	-0.0044(0.0034)	0.19		
Number of alcohol drinks/week				
2	reference			
> 2 but ≤ 6	-0.1906(0.1064)	0.07		
> 6	-0.1078(0.1057)	0.30		
Heavy drinking	-0.0499(0.1089)	0.65		
Years of cocaine use	0.0018(0.0030)	0.70		
Times of cocaine use/day				
1	reference			
> 2 but ≤ 4	0.1037(0.1030)	0.31		
> 4	0.0387(0.1109)	0.72		
Hypertension	-0.0487(0.1219)	0.69		
Diabetes	0.3413(0.2541)	0.18		
hsCRP (mg/dL)	0.0003(0.0114)	0.98		
Systolic BP (mmHg)	-0.0024(0.0026)	0.36		
Diastolic BP (mm Hg)	-0.0056(0.0039)	0.16		
Fasting glucose (mg/dL)	0.0014(0.0019)	0.47		
BMI (kg/m ²)	0.0141(0.0075)	0.06	0.0183(0.0071)	0.01
Total cholesterol (mg/dL)	0.0013(0.0010)	0.21		
HDL-C (mg/dL)	-0.0024(0.0022)	0.28		

Variable	Univariate model		Final multivariate model	
	regression estimate(SE)	p-value	regression estimate(SE)	p-value
Triglycerides (mg/dL)	0.0018(0.0005)	0.0007		
2013 ACC/AHA risk (%)	-0.2923(0.5452)	0.59		
HCV infection	-0.0343(0.0895)	0.70		
Years since HIV was diagnosed	-0.0009(0.0059)	0.87		
CD4 count nadir (cells/mm ³)	0.0005(0.0004)	0.27		
CD4 count at MRS (cells/mm ³)	-0.0001(0.0002)	0.66		
HIV RNA at MRS (copies/mL)	-0.0000(0.0000)	0.27		
Months of NRTI use	0.0009(0.0008)	0.24		
Months of NNRTI use	-0.0010(0.0014)	0.50		
Months of PI use	0.0024(0.0007)	0.0008	0.0027(0.0007)	0.0001

Abbreviations: hsCRP high-sensitivity C-reactive protein; BP blood pressure; glucose fasting glucose; BMI body mass index (kg/m²); LDL-C low density lipoprotein cholesterol; HDL-C high density lipoprotein cholesterol; 2013 ACC/AHA risk cardiovascular risk score based on 2013 ACC/AHA CV risk calculator (Goff et al., 2014); HCV infection persons who were positive for HCV antibodies by 2 enzyme immunoassay were considered to be HCV antibody positive and are hereafter referred to as HCV infected; CD4 count nadir the lowest CD4 count since HIV diagnosis; CD4 count at MRS the CD4 count when magnetic MR spectroscopy was performed; HIV RNA at MRS the HIV viral load when magnetic MR spectroscopy was performed; NRTI nucleoside reverse transcriptase inhibitors; NNRTI non-nucleoside reverse transcriptase inhibitors; PI protease inhibitors.

Table 3

Associations of demographic, laboratory, and clinical factors with myocardial triglyceride by cocaine use status, robust regression analysis.

Variable	Never use of cocaine			Chronic use of cocaine		
	Univariate model		p-value	Final multivariate model		p-value
	regression estimate (SE)			regression estimate (SE)		
Age (year)	-0.0058(0.0066)	0.38		0.0108(0.0081)	0.18	
Male sex	-0.1482(0.1275)	0.25		-0.1981(0.1023)	0.053	0.04
Years of cigarette smoking	-0.0035(0.0042)	0.41		0.0003(0.0041)	0.93	
Number of cigarettes smoked/day						
3	reference			reference		
> 3 but <= 10	0.3179(0.1823)	0.08		-0.1674(0.1159)	0.15	
> 10	-0.2193(0.2118)	0.30		-0.0772(0.1452)	0.60	
Years of alcohol use	-0.0016(0.0048)	0.74		-0.0033(0.0039)	0.40	
Number of alcohol drinks/week						
2	reference			reference		
> 2 but <= 6	0.0627(0.1211)	0.60		-0.2178(0.1255)	0.08	
> 6	0.1323(0.1822)	0.46		-0.1551(0.1203)	0.20	
Heavy drinking	-0.0971(0.2540)	0.70		-0.0837(0.1168)	0.47	
Hypertension	-0.0398(0.1654)	0.81		-0.0516(0.1452)	0.72	
Diabetes	Not estimable			0.3400(0.2520)	0.18	
hsCRP (mg/dL)	0.0050(0.0162)	0.76		-0.0114(0.0141)	0.42	
Systolic BP (mmHg)	0.0018(0.0031)	0.56		-0.0034(0.0032)	0.28	
Diastolic BP (mm Hg)	0.0000(0.0048)	0.99		-0.0069(0.0048)	0.16	
Fasting glucose (mg/dL)	0.0050(0.0064)	0.44		0.0019(0.0019)	0.33	
BMI (kg/m ²)	0.0306(0.0088)	0.0005	0.0306(0.0088)	0.0005	0.0024(0.0092)	0.80
Total cholesterol (mg/dL)	0.0023(0.0017)	0.18		0.0019(0.0012)	0.11	
HDL-C (mg/dL)	0.0091(0.0041)	0.03		-0.0034(0.0025)	0.18	
Triglycerides (mg/dL)	0.0033(0.0012)	0.007		0.0017(0.0006)	0.004	
2013 ACC/AHA risk (%)	-0.1865(0.8558)	0.83		0.8969(0.5006)	0.07	
HCV infection	-0.0488(0.1673)	0.77		0.0003(0.1031)	0.99	
Years since HIV diagnosed	0.0016(0.0075)	0.83		0.0009(0.0070)	0.90	

Variable	Never use of cocaine			Chronic use of cocaine		
	Univariate model		Final multivariate model	Univariate model		Final multivariate model
	regression estimate (SE)	p-value	regression estimate (SE)	regression estimate (SE)	p-value	regression estimate (SE)
CD4 count nadir (cells/mm ³)	0.0004(0.0005)	0.37		0.0003(0.0006)	0.65	
CD4 count at MRS (cells/mm ³)	-0.0001(0.0004)	0.89		-0.0001(0.0002)	0.77	
HIV RNA at MRS (copies/mL)	-0.0000(0.0000)	0.30		-0.0000(0.0000)	0.38	
Months of NRTI use	-0.0011(0.0013)	0.39		-0.0000(0.0010)	0.95	
Months of NNRTI use	-0.0011(0.0015)	0.47		-0.0006(0.0018)	0.73	
Months of PI use	0.0021(0.0008)	0.015		0.0024(0.0010)	0.02	0.0024(0.0011)

Abbreviations: hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; glucose, fasting glucose; BMI, body mass index (kg/m²); LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; 2013 ACC/AHA risk, cardiovascular risk score based on 2013 ACC/AHA CV risk calculator (Goff et al., 2014); HCV infection, persons who were positive for HCV antibodies by 2 enzyme immunoassay were considered to be HCV antibody positive and are hereafter referred to as HCV infected; CD4 count nadir, the lowest CD4 count since HIV diagnosis; CD4 count at MRS, the CD4 count when magnetic MR spectroscopy was performed; HIV RNA at MRS, the HIV viral load when magnetic MR spectroscopy was performed; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

Table 4

Associations of demographic laboratory, and clinical factors with hepatic triglyceride in all study participants, robust regression analysis.

Variable	Univariate model		Final multivariate model	
	regression estimate(SE)	p-value	regression estimate(SE)	p-value
Age (year)	0.0197(0.0143)	0.17		
Male sex	-0.4020(0.2227)	0.07		
Years of cigarette smoking	0.0063(0.0084)	0.45		
Number of cigarettes smoked/day				
3	reference			
> 3 but ≤ 10	0.3445(0.2751)	0.21		
> 10	0.2461(0.3857)	0.52		
Years of alcohol use	-0.0056(0.0088)	0.52		
Number of alcohol drinks/week				
2	reference			
> 2 but ≤ 6	0.7749(0.3208)	0.02		
> 6	0.5549(0.3188)	0.08		
Heavy drinking	0.4401(0.3147)	0.16		
Years of cocaine use	0.0131(0.0123)	0.29		
Times of cocaine use/day				
1	reference			
> 2 but ≤ 4	-0.2903(0.2961)	0.33		
> 4	-0.1349(0.3171)	0.67		
Hypertension	-0.0626(0.3049)	0.84		
Diabetes	-0.5173(0.7030)	0.46		
hsCRP	-0.0160(0.0312)	0.61		
Systolic BP (mmHg)	0.0033(0.0065)	0.61		
Diastolic BP (mm Hg)	0.0138(0.0120)	0.17		
Fasting glucose (mg/dL)	0.0021(0.0049)	0.68		
BMI (kg/m ²)	0.0883(0.0183)	< 0.0001	0.0917(0.0230)	< 0.0001
Total cholesterol (mg/dL)	0.0074(0.0027)	0.007	0.0085(0.0030)	0.004
HDL-C (mg/dL)	0.0068(0.0056)	0.22		

Variable	Univariate model		Final multivariate model	
	regression estimate(SE)	p-value	regression estimate(SE)	p-value
Triglycerides (mg/dL)	0.0060(0.0015)	< 0.0001		
2013 ACC/AHA risk (%)	1.1173(1.2841)	0.38		
HCV infection	0.5523(0.2451)	0.02	0.6278(0.2652)	0.018
Years since HIV diagnosed	0.0014(0.0153)	0.93		
CD4 count nadir (cells/mm ³)	0.0001(0.0010)	0.96		
CD4 count at MRS (cells/mm ³)	0.0006(0.0005)	0.25		
highest HIV RNA (copies/mL)	0.0668(0.0934)	0.47		
HIV RNA at MRS (copies/mL)	-0.0640(0.0519)	0.22		
Months of NRTI use	0.0011(0.0019)	0.58		
Months of NNRTI use	-0.0037(0.0034)	0.27		
Months of PI use	0.0038(0.0020)	0.05		

Abbreviations: hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; glucose, fasting glucose; BMI, body mass index (kg/m²); LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; 2013 ACC/AHA risk, cardiovascular risk score based on 2013 ACC/AHA CV risk calculator (Goff et al., 2014); HCV infection, persons who were positive for HCV antibodies by 2 enzyme immunoassay were considered to be HCV antibody positive and are hereafter referred to as HCV infected; CD4 count nadir, the lowest CD4 count since HIV diagnosis; CD4 count at MRS, the CD4 count when magnetic MR spectroscopy was performed; HIV RNA at MRS, the HIV viral load when magnetic MR spectroscopy was performed; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

Table 5

Associations of demographic, laboratory, and clinical factors with hepatic triglyceride by cocaine use status, robust regression analysis.

Variable	Never use cocaine			Chronic cocaine users		
	Univariate model		p-value	Univariate model		p-value
	regression estimate (SE)			regression estimate (SE)		
Age (year)	0.0030(0.0125)	0.81		0.0113(0.0265)	0.67	
Male sex	-0.3257(0.3219)	0.31		-0.3310(0.3343)	0.32	
Years of cigarette smoking	0.0038(0.0182)	0.83		-0.0018(0.0133)	0.89	
Number of cigarettes smoked/day						
3	reference			reference		
> 3 but ≤ 10	0.2723(0.3184)	0.39		0.1129(0.3817)	0.77	
> 10	-0.7142(0.6843)	0.30		0.4053(0.4854)	0.40	
Years of alcohol use	-0.0062(0.0181)	0.73		0.0113(0.0128)	0.37	
Number of alcohol drinks/week						
2	reference			reference		
> 2 but ≤ 6	0.7437(0.3656)	0.04		0.6947(0.3981)	0.09	
> 6	0.0854(0.4422)	0.84		0.6415(0.3828)	0.09	
Heavy drinking	0.0458(0.4991)	0.92		0.3920(0.3796)	0.30	
Hypertension	-0.3153(0.3650)	0.39		0.1919(0.4522)	0.67	
Diabetes	Not estimable			0.0439(0.8139)	0.95	
hsCRP (mg/dL)	0.0161(0.0450)	0.72		-0.0645(0.0533)	0.23	
Systolic BP (mmHg)	-0.0006(0.0081)	0.94		0.0098(0.0098)	0.32	
Diastolic BP (mm Hg)	-0.0108(0.0115)	0.35		0.0217(0.0147)	0.15	
Fasting glucose (mg/dL)	-0.0011(0.0120)	0.93		0.0037(0.0063)	0.56	
BMI (kg/m ²)	0.0589(0.0261)	0.024	0.046	0.1006(0.0302)	0.0008	
Total cholesterol (mg/dL)	0.0060(0.0036)	0.10		0.0070(0.0036)	0.049	0.0072(0.0034)
HDL-C (mg/dL)	0.0041(0.0097)	0.67		-0.0034(0.0078)	0.66	
Triglycerides (mg/dL)	-0.0020(0.0027)	0.045		0.0068(0.0017)	< 0.0001	
2013 ACC/AHA risk (%)	1.8269(2.0718)	0.37		1.3974(1.7447)	0.42	
HCV infection	1.0792(0.4460)	0.015		0.4194(0.3273)	0.20	
Years since HIV diagnosed	-0.0287(0.0220)	0.19		-0.0100(0.0232)	0.66	

Variable	Never use cocaine			Chronic cocaine users		
	Univariate model		Final multivariate model	Univariate model		Final multivariate model
	regression estimate (SE)	p-value	regression estimate (SE)	regression estimate (SE)	p-value	regression estimate (SE)
CD4 count nadir (cells/mm ³)	−0.0031(0.0024)	0.20		0.0010(0.0012)	0.40	
CD4 count at MRS (cells/mm ³)	0.0012(0.0009)	0.17		−0.0003(0.0007)	0.71	
highest HIV RNA (copies/mL)	0.0364(0.0978)	0.71		0.0273(0.1268)	0.83	
HIV RNA at MRS (copies/mL)	−0.0690(0.0901)	0.44		−0.0558(0.0763)	0.46	
Months of NRTI use	0.0013(0.0016)	0.43		0.0017(0.0032)	0.58	
Months of NNRTI use	−0.0003(0.0031)	0.91		−0.0066(0.0055)	0.22	
Months of PI use	0.0019(0.0016)	0.23		0.0076(0.0033)	0.021	0.0070(0.0006)

Abbreviations: hsCRP, high-sensitivity C-reactive protein; BP, blood pressure; glucose, fasting glucose; BMI, body mass index (kg/m²); LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; 2013 ACC/AHA risk, cardiovascular risk score based on 2013 ACC/AHA CV risk calculator (Goff et al., 2014); HCV infection, persons who were positive for HCV antibodies by 2 enzyme immunoassay were considered to be HCV antibody positive and are hereafter referred to as HCV infected; CD4 count nadir, the lowest CD4 count since HIV diagnosis; CD4 count at MRS, the CD4 count when magnetic MR spectroscopy was performed; HIV RNA at MRS, the HIV viral load when magnetic MR spectroscopy was performed; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.