Comprehensive Cardiac Magnetic Resonance Imaging and Spectroscopy Reveal a High Burden of Myocardial Disease in HIV Patients

Cameron J. Holloway, FRACP, DPhil; Ntobeko Ntusi, MBBS, DPhil; Joseph Suttie, FRACP, DPhil; Masliza Mahmod, MRCP, DPhil; Emma Wainwright, MBBS; Genevieve Clutton, DPhil; Gemma Hancock, DPhil; Philip Beak, BA; Abdelouahid Tajer, PhD; Stefan K. Piechnik, PhD; Jurgen E. Schneider, DPhil; Brian Angus, FRCP; Kieran Clarke, PhD; Lucy Dorrell, MBBS, PhD; Stefan Neubauer, MD

Background—HIV infection continues to be endemic worldwide. Although treatments are successful, it remains controversial whether patients receiving optimal therapy have structural, functional, or biochemical cardiac abnormalities that may underlie their increased cardiac morbidity and mortality. The purpose of this study was to characterize myocardial abnormalities in a contemporary group of HIV-infected individuals undergoing combination antiretroviral therapy.

Methods and Results—Volunteers with HIV who were undergoing combination antiretroviral therapy and age-matched control subjects without a history of cardiovascular disease underwent cardiac magnetic resonance imaging and spectroscopy for the determination of cardiac function, myocardial fibrosis, and myocardial lipid content. A total of 129 participants were included in this analysis. Compared with age-matched control subjects (n=39; 30.23%), HIV-infected subjects undergoing combination antiretroviral therapy (n=90; 69.77%) had 47% higher median myocardial lipid levels (P<0.003) and 74% higher median plasma triglyceride levels (both P<0.001). Myocardial fibrosis, predominantly in the basal inferolateral wall of the left ventricle, was observed in 76% of HIV-infected subjects compared with 13% of control subjects (P<0.001). Peak myocardial systolic and diastolic longitudinal strain were also lower in HIV-infected individuals than in control subjects and remained statistically significant after adjustment for available confounders.

Conclusions—Comprehensive cardiac imaging revealed cardiac steatosis, alterations in cardiac function, and a high prevalence of myocardial fibrosis in a contemporary group of asymptomatic HIV-infected subjects undergoing combination antiretroviral therapy. Cardiac steatosis and fibrosis may underlie cardiac dysfunction and increased cardiovascular morbidity and mortality in subjects with HIV. (Circulation. 2013;128:814-822.)

Key Words: fibrosis ◼ heart function tests ◼ HIV-1 ◼ imaging, diagnostic ◼ myocardial fibrosis

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From the Department of Physiology, Anatomy, and Genetics (C.J.H., K.C.), and Oxford NIHR Biomedical Research Centre (E.W., G.C., G.H., S.K.P., B.A., L.D., S.N.), University of Oxford, Oxford, United Kingdom; University of Oxford Centre for Clinical Magnetic Resonance Research, Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford, United Kingdom (C.J.H., N.N., J.S., M.M., P.B., S.K.P., J.E.S., S.N.); St. Vincent’s Hospital, Darlinghurst, Sydney, Australia (C.H.); and Centre for Statistics in Medicine, Wolfson College Annexe, Oxford, United Kingdom (A.T.).

*Drs Dorrell and Neubauer are joint senior authors of this work.

Correspondence to Cameron Holloway, FRACP, DPhil, St. Vincent’s Hospital, Victoria St. Darlinghurst, NSW 2010, Australia. E-mail cholloway@stvincents.com.au

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and noninfectious causes; the direct effects of HIV infection, including increased circulating proinflammatory cytokines; and complications of cART, such as abnormal fat metabolism.

**Clinical Perspective on p 822**

Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) techniques allow the concurrent determination of cardiac contractile function, fibrosis, and fat metabolism and thus offer the potential to obtain a highly accurate and sensitive assessment of multiple structural, functional, and biochemical cardiac parameters. We report on the first comprehensive study to use cardiac MRI and MRS in asymptomatic HIV patients receiving effective cART, to determine the prevalence and extent of myocardial abnormalities.

**Methods**

**Study Subjects**

Subjects with HIV infection undergoing cART (n=90) were recruited during 2011 and 2012 to an observational study from 4 HIV centers in Oxfordshire, United Kingdom. Inclusion criteria were age ≥18 years with no history of cardiovascular disease, hepatitis C, or injection drug use and no contraindications to cardiac magnetic resonance (MR) assessment. All subjects fulfilling these criteria from the outpatient centers were invited to participate, and the first 90 responders were included. The study was approved by the Oxfordshire Research Ethics Committee (institutional review board reference No. 10/H0604/95), and all subjects gave written informed consent before enrollment. All HIV-seropositive subjects had initiated cART in accordance with national treatment guidelines. A control group that comprised healthy subjects matched for age and ethnicity (self-defined) and with low risk of HIV infection (n=39) was studied contemporaneously. Early morning assessments took place at the University of Oxford Center for Clinical Magnetic Resonance Research after an overnight fast. Both MRI and MRS scans and blood tests were performed during a 3-hour fasting visit. All analyses were performed in a blinded manner, with sequential numbering of subjects, with HIV status revealed only after analysis was complete.

**Body Mass and Metabolic Marker Assessments**

Height, weight, hip, and waist circumference were recorded. Body fat percentages, water percentages, and lean body weights were measured with a bioimpedance analyzer (Bodystat Ltd, Douglas, Isle of Man). For measurement of subcutaneous and visceral fat, transverse abdominal images were acquired with a single breath-hold, 1-slice, water-suppressed, T1-weighted turbo spin echo sequence centered on L4 at 3-T MRI, using a modified sequence, based on previous similar acquisitions. Images were manually contoured for subcutaneous and visceral fat volume by use of standard Siemens workstation analysis.

A fasting blood sample was obtained for measurement of plasma glucose, free fatty acids, and cholesterol. Insulin was measured with ELISA (Mercodia AB, Uppsala, Sweden). To calculate the homeostasis model assessment for insulin resistance, the following formula was used: Fasting insulin (pmol/L) x fasting glucose (mmol/L)/135.3

**1H-MR Spectroscopy**

All 1H-MRS studies were performed on a 3-T MR scanner (Tim Trio, Siemens Healthcare, Erlangen, Germany). The 1H-MRS sequence was based on a conventional stimulated echo-acquisition mode sequence that was modified to achieve a short echo time of 10 ms, as described previously. A voxel, or area of interest, was placed in a midventricular slice in the interventricular septum of a short-axis image (Figure 1). Cardiac gated spectra were acquired as described previously. Acquisition consisted of 6 breath holds of approximately 16 seconds each. Of these, 5 breath holds allowed for the acquisition of the 35 nonaveraged water-suppression spectra. Four nonaveraged water spectra were acquired with a minimum repetition time of 4 seconds in a separate breath hold with the water-suppression radiofrequency pulse power set to zero. Spectra were analyzed with MATLAB and the AMARES algorithm included in the jMRUI package 4, as described previously. An example of a proton MRS cardiac spectrum is shown in Figure 1C. Previous studies in our department have demonstrated good reproducibility with this single breath-hold method, with a 19% coefficient of variance.

**Measurement of Cardiac Volumes, Mass, and Function**

Left and right ventricular cardiac volumes, mass, and function were assessed by cardiac MRI in a 1.5-T Avanto MR system (Erlangen,
Germany) as described previously. A stack of steady-state free-precession short-axis cine images were obtained with breath hold and cardiac gating with subsequent analysis of cardiac volumes and function by use of Argus processing (Siemens Medical Solutions, Erlangen, Germany). Cardiac MR is considered the gold standard for assessment of cardiac function with excellent reproducibility.

**Myocardial Tagging**

Semiautomated analysis was performed with CIM software (CIMTag2D version 7, Auckland MRI Research Group, Auckland, New Zealand) by aligning a grid to the myocardial tagging planes in end diastole. End systole was determined visually, and tags were adjusted at each frame throughout the cardiac cycle. A 4-chamber horizontal long-axis and a mid-short-axis image were acquired for each subject. From the mid-short-axis image, peak systolic and diastolic circumferential strain rates were derived. From the horizontal long-axis view, peak systolic and diastolic longitudinal strain rates were determined.

**Assessment of Myocardial Fibrosis With Late Gadolinium Enhancement and T1 Mapping**

Late gadolinium enhancement cardiac MR was performed with a T1-weighted segmented inversion recovery turbo fast low-angle shot sequence (echo time 4.8 ms, voxel size 1.4×2.4×7 mm, flip angle 20°) after a 6-minute delay after the administration of 0.1 mmol/kg gadolinium contrast agent (Dotarem [gadoterate meglumine]). The inversion time was adjusted for optimal nulling of normal myocardium. All images were analyzed with in-house software written in IDL (Interactive Data Language, version 6.1, Exelis Visual Information Solutions, Inc, Boulder, CO). Myocardial contours were drawn semiautomatically (C.H. and N.N.); then, 2 forms of analysis were performed. First, visual analysis was performed in which 2 experienced operators scored the presence or absence of fibrosis on blinded data. In addition, quantitative analysis for scar percentage was performed with IDL software. Although myocardial contours were derived by the program, some contours required adjustment to ensure only myocardium was included in the analysis. The program then produced values for scar size (%) and T1 values. T1 mapping was performed with a short modified Look-Locker inversion recovery technique in which adjustment for heart rate is not required. Adjustment for heart rates was performed during acquisition. Quality assessment of T1 maps and late gadolinium images was performed as described previously.

**Statistical Analysis**

No formal sample-size calculation was performed because the study was conceived as exploratory. Data were summarized as medians and interquartile range for continuous variables and numbers and percentages for discrete variables. Wilcoxon–Mann–Whitney test (for continuous variables) and χ² (for categorical variables) tests were used to explore whether there were differences between the HIV group and control group with respect to cardiac function variables and in cardiovascular risk factors.

To further explore the association between HIV status as the independent variable and the cardiac function variables (myocardial fat, ejection fraction, cardiac relaxation, circumferential systolic strain, peak circumferential diastolic strain rate, longitudinal systolic strain, and peak longitudinal diastolic strain rate), separate median regression models were used, with the control subjects group included as a reference category. Median regression analyses were conducted with the Stata (StataCorp LP, College Station, TX) command qreg, qreg fits quantile (including median) regression models, also known as least absolute value models. The quantile regression models fit by qreg in Stata express the quantiles (in the present case, the median) of the conditional distribution as linear functions of the independent variables. This is a similar approach to multiple linear regression, which analyzes the mean. Median regression relaxes the normality assumption of the residuals required in multiple linear regression. All regression models were adjusted for available known confounders, i.e., high-density lipoprotein cholesterol, glucose, smoking, visceral fat, age, sex, and ethnicity. Results from median regression models were presented as β-coefficients, which represent the average difference in an outcome, and 95% confidence intervals. Statistical analyses were performed with Stata version 12.1.

**Results**

All subjects, regardless of HIV status, were asymptomatic without a history of chest pain or dyspnea (all were New York Heart Association class I). Two patients with HIV were unexpectedly found to have subendocardial myocardial infarction on cardiac MR, so all their data were excluded from subsequent analysis.

**Participant Characteristics**

HIV-seropositive subjects had diagnosed infection for a mean (SD) of 7.44 (6.01) years. Among all HIV subjects, 84% had plasma viremia consistently suppressed to <50 copies/mL. Of those who were not virologically suppressed, 27% had initiated cART within the preceding 6 months. cART regimens included a nonnucleoside reverse transcriptase inhibitor or ritonavir-boosted protease inhibitor in 68% and 32% subjects, respectively. Mean CD4⁺ cell counts at enrollment were 546 (179) cells/µL. Pre-antiretroviral therapy CD4⁺ cell nadir was <200 cells/µL in 55% of patients. Patients and control subjects had, on average, similar ages and traditional cardiovascular risk factors. No participant had a history of diabetes mellitus. Fourteen subjects with HIV (15%) and 6 control subjects (15%) had a history of treated hypercholesterolemia. Fourteen percent of HIV subjects and 15% of control subjects were taking medications for cholesterol; 8 subjects with HIV (9%) were taking statins, and 4 (4%) were taking fibrates. By comparison, 6 control subjects (15%) were taking statins, but none were taking fibrates. Hypertension was reported in 14 subjects with HIV (15%) and 4 control subjects (10%). A family history of coronary artery disease was reported in 13 subjects with HIV (14%) and 7 control subjects (18%; all P>0.05). Control subjects were recruited by local advertising. Because of local ethics requirements, the HIV status of control subjects was not confirmed by testing, and their negative status was self-declared only. Characteristics of the study subjects by HIV status (HIV and control subjects groups) are shown in Table 1.

**Weight and Metabolic Markers**

There were no significant differences in total body weight, waist circumference, body mass index, lean body weight, body fat composition, or hip measurements between HIV-infected and control subjects, nor was there any significant difference in subcutaneous and visceral fat as determined by MR at L4 (Table 1). Rates of metabolic syndrome (according to the 2006 International Diabetes Federation consensus worldwide definition) were not statistically different between the 2 groups (22.73% in HIV subjects versus 15.38% in control subjects, P=0.34).

HIV-infected subjects had lower median high-density lipoprotein cholesterol (1.10 [0.90, 1.30] versus 1.30 [0.90, 1.70] mmol/L, P=0.03), higher total cholesterol/high-density lipoprotein ratios (4.20 [3.08, 5.05] versus 3.55 [2.72, 4.00], P=0.02), and a 74% increase in median plasma triglycerides (1.22 [0.87, 1.77] mmol/L versus 0.70 [0.56, 1.05] mmol/L, P<0.001) compared with control subjects, whereas total and low-density lipoprotein cholesterol (1.77 mmol/L versus 0.70 [0.56, 1.05] mmol/L, P<0.001) were lower in HIV-infected subjects compared with control subjects.
lipoprotein cholesterol levels were not statistically different between the 2 groups (Table 1). Median plasma glucose was marginally higher in the HIV cohort (5.30 [4.50, 5.80] versus 4.80 [4.50, 5.30] mmol/L, \( P = 0.04 \)), but mean levels of insulin and free fatty acids in the 2 groups were not statistically different (Table 1). Six patients (7%) in the HIV group had impaired glucose tolerance, defined as a fasting glucose \( \geq 6.1 \) to 6.9 mmol/L (110–125 mg/dL), and 4 (4%) had fasting glucose >7.0 mmol/L (126 mg/dL, all <8.0 mmol/L). By comparison, 2 subjects (5%) had fasting glucose in the 6.1 to 6.9 mmol/L range, and no control subject had a fasting glucose in the diabetic range.

Myocardial Lipids
Median myocardial lipid levels were elevated by 47% in the HIV group compared with the control subjects (0.53 [0.30, 0.85] versus 0.36 [0.21, 0.55], \( P < 0.003 \); Table 1), and this was independent of serum triglyceride levels. Median regression modeling confirmed the significant association between HIV and

<table>
<thead>
<tr>
<th>Table 1. Subject Characteristics by HIV Status</th>
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<tbody>
<tr>
<td>HIV Infected (n=90)</td>
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<tr>
<td><strong>Demographic and blood pressure measurements</strong></td>
</tr>
<tr>
<td>Males</td>
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<tr>
<td>White or European ancestry</td>
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<tr>
<td>Metabolic syndrome†</td>
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<td>Age, y</td>
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<tr>
<td>Smoking, pack-years</td>
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<tr>
<td>Systolic BP, mm Hg</td>
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<td>Diastolic BP, mm Hg</td>
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<td><strong>Anthropometric measurements</strong></td>
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<td>Height, m</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<td>Lean body weight, kg</td>
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<tr>
<td>% Body fat</td>
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<td>Subcutaneous fat, cm²</td>
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<td>Waist circumference, cm</td>
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<tr>
<td>Hip circumference, cm</td>
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<tr>
<td>Visceral fat, cm²</td>
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<td><strong>Plasma metabolites</strong></td>
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<td>Total cholesterol, mmol/L</td>
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<td>HDL cholesterol, mmol/L</td>
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<td>LDL cholesterol, mmol/L</td>
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<td>Cholesterol/HDL ratio</td>
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<td>Triglycerides, mmol/L</td>
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<td>Glucose, mmol/L</td>
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<td>Insulin, mU/L</td>
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<td>Free fatty acids, mmol/L</td>
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<tr>
<td><strong>Cardiac parameters</strong></td>
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<tr>
<td>Myocardial lipids, %</td>
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<tr>
<td>Left ventricular ejection fraction, %</td>
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<tr>
<td>Adjusted LV end-diastolic volume, mL/BSA</td>
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<tr>
<td>Adjusted LV end-systolic volume, mL/BSA</td>
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<tr>
<td>Adjusted LV stroke volume, mL/BSA</td>
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<tr>
<td>Circumferential systolic strain, %</td>
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<tr>
<td>Peak circumferential diastolic strain rate, %/s</td>
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<tr>
<td>Longitudinal systolic strain, %</td>
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<td>Peak longitudinal diastolic strain rate, %/s</td>
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<tr>
<td>T1 mapping shMOLLI value, ms</td>
</tr>
<tr>
<td>Late gadolinium enhancement, 3sd</td>
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<td>Presence of late gadolinium enhancement</td>
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</table>

Data are median (interquartile range) for continuous variables or n (%) for categorical variables. 3sd indicates three standard deviations; BP, blood pressure; BSA, body surface area; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; and shMOLLI, short modified Look-Locker inversion recovery.

*Wilcoxon–Mann–Whitney test for continuous variables (rank-sum command in Stata) and \( \chi^2 \) test for categorical variables.

†The International Diabetes Federation consensus worldwide definition of the metabolic syndrome (2006) was used.
Table 2. Association Between Cardiac Function and Presence of HIV: Linear Regression Models to Demonstrate the Association Between Outcome Variables With HIV Status as an Independent Predictor After Adjustment for Risk Factors*

<table>
<thead>
<tr>
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<th>β (95% CI), Median Regression</th>
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<tbody>
<tr>
<td>Myocardial fat</td>
<td>0.27 (0.04 to 0.510)†</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>−2.38 (−5.61 to 0.860)</td>
</tr>
<tr>
<td>Circumferential systolic strain</td>
<td>1.46 (0.30 to 2.618)‡</td>
</tr>
<tr>
<td>Peak circumferential diastolic strain rate</td>
<td>−16.14 (−26.09 to −6.197)‡</td>
</tr>
<tr>
<td>Longitudinal systolic strain</td>
<td>1.27 (0.10 to 2.440)†</td>
</tr>
<tr>
<td>Peak longitudinal diastolic strain rate</td>
<td>−13.72 (−26.54 to −0.893)†</td>
</tr>
</tbody>
</table>

β -coefficients represent the average difference between HIV patients and control subjects (reference: control subjects). † Indicates β-coefficient; and CI, confidence interval.

*Adjusted for high-density lipoprotein cholesterol, glucose, smoking, visceral fat, age, sex, and ethnicity.

†P<0.05; ‡P<0.01;

myocardial steatosis: Subjects with HIV had significantly higher mean levels of myocardial fat (adjusted β-coefficient=0.27, 95% confidence interval 0.04–0.51; Table 2).

Association Between Cardiac Function and HIV Status

In multiple linear regression models (adjusted for high-density lipoprotein cholesterol, glucose, smoking, visceral fat, age, sex, and ethnicity), the association between HIV and alterations in myocardial tagging parameters remained statistically significant (Table 2).

Patchy and Diffuse Myocardial Fibrosis in HIV

Late gadolinium enhancement imaging MR techniques demonstrated that 76% of HIV-infected subjects had evidence of patchy myocardial fibrosis on visual assessment. All but 1 of these had patchy fibrosis in a midwall and subepicardial distribution in the basal inferolateral wall (Figure 2). This is a typical pattern that suggests previous myocarditis. In addition, 15% of HIV-infected subjects had scar in the basal septum. By comparison, only 13% of control subjects had evidence of any myocardial fibrosis. As mentioned previously, 2 HIV-seropositive subjects had subendocardial myocardial infarction and subsequently epicardial coronary disease confirmed at angiography, and these subjects were excluded from the analyses. No subjects in the control group had evidence of infarction. By volumetric analysis methods, the burden of left ventricular patchy fibrosis was 3.97% (2.27%, 6.20%) in the HIV-infected cohort compared with 1.87% (0.99%, 3.49%) in control subjects (P<0.001; Figure 3).

There was no association between duration of diagnosed HIV infection, recent CD4 count or viral load, or pretherapy CD4 nadir with the alterations in cardiac function parameters, cardiac steatosis, or measures of myocardial fibrosis.

Discussion

This is the first study to provide an extensive assessment of cardiac structure, function, and metabolism using MR in asymptomatic HIV-seropositive patients. In this cross-sectional analysis, the major findings were cardiac steatosis, in association with deranged plasma lipids, altered myocardial function, and a high rate of myocardial fibrosis in nearly all patients with treated HIV infection. These metabolic and structural cardiac abnormalities have not been reported previously and may in part explain the cardiac functional abnormalities and increased mortality reported in subjects receiving cART.13

Although plasma metabolic derangements have been well described in the era of cART,14 the present study is the first to demonstrate cardiac steatosis in HIV subjects. We hypothesize that cardiac steatosis is a sequela of cART-induced hyperlipidemia and dysglycemia, although prospective studies before and after cART are needed to test this theory. The association between treated HIV infection and myocardial fat remained after adjustment for potential known confounders. The extent of cardiac steatosis we observed in subjects with HIV did not quite reach cardiac fat levels reported in obese and diabetic individuals,15,16 although it was considerably higher than observed in control subjects within our center. The heart does not store lipid, in contrast to other organs such as the liver, and cardiac fat rarely exceeds 2% even in significant disease. The extent of cardiac steatosis found in the present study is of uncertain clinical significance, but given its possible association with antiretroviral drugs to which patients may be continuously exposed for several decades, this warrants further investigation. The elevated myocardial lipid level in subjects with HIV was accompanied by plasma lipid abnormalities that were of similar magnitude to those reported in previous studies in HIV cohorts,12 and a causal relationship is certainly plausible given the link between plasma and cardiac lipid abnormalities in other diseases, such as diabetes mellitus and obesity. We did not find any significant association between classes of antiretroviral drugs and alterations in cardiac steatosis, although the present study was not adequately powered to show this. Larger prospective studies are needed to determine the role of individual medications and combinations of therapies. The present study was not designed to assess extracardiac fat, so further studies are needed to determine whether extracardiac fat in these subjects correlates with myocardial steatosis.

Positron emission tomography has demonstrated no changes in myocardial fatty acid uptake, esterification, and utilization...
in HIV-positive subjects compared with control subjects.\textsuperscript{17} We have extended these observations, with the present data showing increased storage of fat in the myocardium in patients with HIV undergoing cART. Long-term exposure to antiretroviral medications can confer a substantial metabolic risk for a large proportion of patients with HIV, with up to half having dyslipidemias and one third having impaired glucose tolerance, which further compounds cardiovascular risk.\textsuperscript{18} Peripheral metabolic complications in other diseases such as diabetes mellitus and obesity are associated with increased cardiac functional derangements, morbidity, and mortality, which are independent of blood pressure, body mass index, and coronary disease.\textsuperscript{19,20} Whether lipid and glucose abnormalities predispose to cardiac functional alterations in HIV is unknown.

The high prevalence of myocardial fibrosis in the HIV group provides a second potential mechanism for altered cardiac function in the HIV population. The vast majority of patients with HIV had evidence of patchy myocardial fibrosis in the basal inferolateral wall of the left ventricle. Although this pattern of myocardial fibrosis is not specific for a single cause, it likely represents previous myocarditis.\textsuperscript{21} In studies before the advent of cART, myocarditis was revealed

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on biopsy in the vast majority of HIV patients with dilated cardiomyopathy. However, to the best of our knowledge, subclinical myocarditis has not been widely reported in the cART era. The present data may represent subclinical myocarditis in most people with HIV despite effective cART. It is important to appreciate that although there was a 6-fold difference in fibrosis prevalence between groups (13% versus 76%, control versus HIV), there was only a 2.1% difference in scar burden between groups. We believe this highlights that although scar prevalence is high, the volume of fibrosis is low. In addition, residual scar burden from myocarditis of all causes is usually low. The cause of myocarditis in this group is unknown, but given that fibrosis was observed in nearly all HIV patients, the findings may either represent myocardial inflammation during primary HIV infection, a chronic inflammatory response, or a healed scar. Increased overall T1 mapping values compared with control subjects were also observed, which may also reflect myocardial fibrosis, although this association requires further confirmation. Of note, myocardial T1 values were elevated despite the increased myocardial fat demonstrated on proton spectroscopy, which would be expected to decrease T1 values, further supporting the concept of diffuse myocardial fibrosis in these patients. Regardless of the cause, given the well-established association of myocardial scarring with morbidity and mortality in cardiomyopathy, measured by cardiac MR, HIV-related cardiac fibrosis could indicate a potential increased risk of cardiac morbidity. This hypothesis warrants further investigation in longitudinal studies. We did not acquire post-contrast T1 images in the present study, although this would be of interest in further work.

Our findings of altered myocardial function in patients with HIV are consistent with previous echocardiography studies demonstrating systolic and diastolic dysfunction in asymptomatic subjects undergoing cART. We have confirmed and extended these findings using the gold standard for cardiac functional assessment, cardiac MRI. We propose that cardiac steatosis, secondary to cART, and myocardial fibrosis may underlie the dysfunction observed. It is conceivable that in addition to the known increased incidence of HIV-related coronary disease, cardiac steatosis and fibrosis may partially underlie the increased cardiac morbidity and mortality seen in this group.

Because the clinical implications of the present results have yet to be determined, and MRS is not yet a clinical tool, we do not advocate the use of cardiac MR scans for the routine assessment of asymptomatic subjects with HIV. We believe the findings are hypothesis generating and may help develop further studies to determine the pathogenesis of early cardiac disease in patients with treated HIV. Recently, the concept of HIV-induced premature aging has been proposed as a mechanism for changes in cardiac pathological findings. This hypothesis is not supported by the present data, because the extent of cardiac steatosis, the near-universal finding of...
myocardial fibrosis, and the reduction in systolic strain are not characteristic features of the aging heart.27

Study Limitations

This study was cross-sectional and exploratory, so it is not possible to assign causal links between cART, cardiac steatosis, fibrosis, and the altered function seen in the HIV group. Although cART has been associated with lipid abnormalities and is a plausible explanation for cardiac steatosis in the present study, HIV itself has been modestly associated with deranged lipid metabolism, and diet and genetic factors were not accounted for as potential confounders in the present study. Dysglycemia or diabetes mellitus may be expected to affect the MRI results, including the higher rate of late gadolinium enhancement, abnormal T1 mapping, and steatosis. Although the statistics accounted for glucose measurements, a single glucose measurement may incompletely control for the effects of chronic dysglycemia, which is more prevalent in patients with HIV. In addition, we did not measure perfusion abnormalities in the HIV group; a greater burden of coronary disease in this group may account for some of the functional changes.5 Larger prospective studies in subjects undergoing cART and those who are CART-naive are required to determine at what stage cardiac steatosis, fibrosis, or dysfunction occurs and to determine any direct effect of HIV itself. In addition, given the diverse combinations of antiretroviral drugs used by patients in the present study, we were not able to identify drug- or drug class–specific effects; this would necessitate a suitably powered prospective study. Self-reporting of negative HIV status in control subjects was an additional limitation of the present study, although any false status may have demonstrated a greater difference between the 2 groups. Because of multiple testing concerns in the present study, all findings are interpreted as hypothesis generating and require confirmation in larger cohorts.

Conclusions

In the present study, we have demonstrated a previously unappreciated high burden of metabolic, structural, and functional abnormalities in HIV subjects undergoing cART using cardiac MRI and MRS. Although the clinical implications of these findings are uncertain, the present study generates the hypothesis that these abnormalities, in addition to coronary disease, account for the increased cardiac morbidity and mortality observed in people living with chronic HIV infection, and larger prospective studies are needed to address this further.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Infection with HIV is a major public health interest in both the developed and developing world, with a worldwide prevalence of more than 33 million people. With the advent of combined antiretroviral therapy, HIV has become a treatable condition. However, individuals with HIV have a high incidence of cardiovascular disease, arising in part as a metabolic complication of long-term treatment. The present report represents the first literature to comprehensively explore changes in human cardiac structure, function, and metabolism as a consequence of treated HIV. Using the powerful imaging techniques of cardiac MRI and MRS, we demonstrated that patients with HIV infection have >50% elevation in myocardial lipids, a near-universal rate of diffuse patch myocardial fibrosis, and alterations in cardiac function. In a contemporary group of people with treated HIV, cardiac steatosis and fibrosis may not only underlie the alterations in cardiac function but may also underlie the increased cardiac morbidity and mortality. We believe there is an urgent need to understand the pathophysiology of cardiac complications to enable effective therapies and prevention of cardiac disease in patients with chronic HIV.
Comprehensive Cardiac Magnetic Resonance Imaging and Spectroscopy Reveal a High Burden of Myocardial Disease in HIV Patients
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