HIV and AIDS pose a major global public health challenge. In 2014, 35 million people globally were living with HIV, with 2.1 million new infections. \(^1,2\) The survival of people living with HIV/AIDS has dramatically increased since the widespread use of antiretroviral therapy (ART)\(^3\) and, consequently, HIV treatment has evolved to include management of long-term comorbidities, including cardiovascular disease (CVD).\(^4\)

**Background**—Patients with treated HIV infection have clear survival benefits although with increased cardiac morbidity and mortality. Mechanisms of heart disease may be partly related to untreated chronic inflammation. Cardiovascular magnetic resonance imaging allows a comprehensive assessment of myocardial structure, function, and tissue characterization. We investigated, using cardiovascular magnetic resonance, subclinical inflammation and myocardial disease in asymptomatic HIV-infected individuals.

**Methods and Results**—Myocardial structure and function were assessed using cardiovascular magnetic resonance at 1.5-T in treated HIV-infected individuals without known cardiovascular disease (n=103; mean age, 45±10 years) compared with healthy controls (n=92; mean age, 44±10 years). Assessments included left ventricular volumes, ejection fraction, strain, regional systolic, diastolic function, native T1 mapping, edema, and gadolinium enhancement. Compared with controls, subjects with HIV infection had 6% lower left ventricular ejection fraction (\(P<0.001\)), 7% higher myocardial mass (\(P=0.02\)), 29% lower peak diastolic strain rate (\(P<0.001\)), 4% higher short-tau inversion recovery values (\(P=0.02\)), and higher native T1 values (969 versus 956 ms in controls; \(P=0.01\)). Pericardial effusions and myocardial fibrosis were 3 and 4× more common, respectively, in subjects with HIV infection (both \(P<0.001\)).

**Conclusions**—Treated HIV infection is associated with changes in myocardial structure and function in addition to higher rates of subclinical myocardial edema and fibrosis and frequent pericardial effusions. Chronic systemic inflammation in HIV, which involves the myocardium and pericardium, may explain the high rate of myocardial fibrosis and increased cardiac dysfunction in people living with HIV. *(Circ Cardiovasc Imaging. 2016;9:e004430. DOI: 10.1161/CIRCIMAGING.115.004430.)*

**Key Words:** cardiac function ■ endomyocardial fibrosis ■ HIV-1 ■ HIV-associated cardiovascular disease ■ magnetic resonance imaging ■ pericardial effusion

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**HIV-1–Related Cardiovascular Disease Is Associated With Chronic Inflammation, Frequent Pericardial Effusions, and Probable Myocardial Edema**

Ntobeko Ntusi, DPhil; Eoin O’Dwyer, MBChB; Lucy Dorrell, MBBS, PhD; Emma Wainwright, MBBS; Stefan Piechnik, PhD; Genevieve Clutton, DPhil; Gemma Hancock, DPhil; Vanessa Ferreira, MD, DPhil; Pete Cox, MD, DPhil; Motasim Badri, PhD; Theodoros Karamitsos, MD, PhD; Sam Emmanuel, BSc; Kieran Clarke, PhD; Stefan Neubauer, MD; Cameron Holloway, DPhil

**See Editorial by Hsue and Tawakol**

**See Clinical Perspective**

The link between HIV infection and CVD was established early in the history of the AIDS epidemic.\(^5\) ART has led to a reduced incidence of myocardial disease; yet, treated individuals continue to have a high incidence of myocardial pathology compared with HIV-uninfected people. Although

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***Cardiomyopathies***

**HIV-1–Related Cardiovascular Disease Is Associated With Chronic Inflammation, Frequent Pericardial Effusions, and Probable Myocardial Edema**

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the pathophysiology of cardiac disease in HIV has not been well defined, it is likely multifactorial, including direct effects of the virus, opportunistic infections, and ART.6–9

Cardiovascular magnetic resonance (CMR) imaging allows a comprehensive assessment of myocardial structure, function, and tissue characterization. We have previously reported, in a cohort of asymptomatic treated patients with HIV, findings of increased cardiac steatosis and myocardial regional fibrosis although these findings did not fully explain the extent of myocardial dysfunction.10 Our observations have been replicated by Thiera et al.11 In this study, we used our previous cohort and an additional 66 subjects, including a group naive to ART, and we investigated whether there is an association between myocardial inflammation in subjects with HIV and cardiac pathology.

Methods

Study Population

Subjects with HIV on ART (n=90) and subjects with HIV naive to ART treatment (n=13) were recruited into a cross-sectional, observational study of CVD in HIV infection from 4 HIV treatment centers in the United Kingdom. We previously published the initial results from this study and have expanded on these results by adding 66 subjects, including 13 patients with HIV naive to ART.10 Subjects included in the study were older than 18 years and had a confirmed diagnosis of HIV. Exclusion criteria included contraindications to CMR, nonsinus rhythm, known CVD (previous myocardial infarction, previous myocarditis, heart failure, arrhythmia, or other chronic cardiac conditions), a history of hepatitis C or immune activation to gadolinium. Healthy volunteers (n=92) with no history of cardiac disease or HIV infection and with a normal ECG underwent CMR as controls. All subjects gave written informed consent to participate in the study. Ethical approval was granted by the Oxford Research Ethics Committee (REC Ref 10/H0604/95). Treated HIV seropositive subjects were treated in accordance with UK treatment guidelines. Assessments, including CMR, were carried out in the University of Oxford Centre for Clinical Magnetic Resonance Research. All analyses were performed in a blinded manner, with sequential numbering of subjects, with HIV status revealed only after analysis was complete.

CMR Image Acquisition

CMR studies were performed using a single 1.5-T MR system (Avanto; Siemens Healthcare, Erlangen, Germany). T1 mapping was performed using the shortened modified look-locker inversion recovery sequence, and T2-weighted-CMR was performed with the black blood short-tau inversion recovery (STIR) sequence, as previously published.10–14 Late-gadolinium enhancement (LGE) imaging and T2W-CMR was performed with the black blood short-tau inversion recovery (STIR) sequence, as previously published.13

CMR Image Analysis

All CMR images were analyzed offline in a blinded fashion. Analysis of left ventricular (LV) volumes, mass, and ejection fraction was performed using Argus software (Version VB17, 2011, Siemens Medical Solutions) as previously described.16

Tagged Cine Images

Postprocessing and semiautomated analysis were performed using CIM software (CIMTag2D, version 7, Auckland, New Zealand) by aligning a grid to the myocardial tagging planes in end diastole.

STIR Images

Quantitative analysis was performed by comparing the LV myocardium in the short axis against adjacent skeletal muscle in the same slice, as previously published.13

T1 Mapping

Analysis of T1 mapping was performed as previously described.10

LGE Images

Images were evaluated qualitatively for the presence or absence, pattern (subendocardial, midwall, subepicardial, and transmural), and regional distribution of LGE areas by 2 observers (N.N. and C.H.), each with at least 3 years of CMR experience, who were blinded to the rest of the data. Volume fraction of LGE was calculated using a threshold of 2SDs.

Areas of Myocardial Involvement by STIR and Precontrast T1 Mapping

On dark-blood T2W images, edema was diagnosed when myocardial T2 SI is ≥1.9 compared with that of skeletal muscle.15 On T1 maps, myocardial injury was diagnosed when T1 was >900 ms (which is >2SDs above the mean T1 value at 1.5T), as previously published for the objective detection of acute myocardial edema.16 For all quantitative analyses of T2-weighted and T1 map images, only regions of myocardium with a contiguous area of ≥40 mm² above the specified thresholds were considered relevant. This corresponds to 10 pixels for the STIR method11 to reduce the detection of noise as positive findings. To calculate the extent of myocardial involvement in a subject detected by the tissue characterization techniques, the percentage of abnormal myocardium as defined above was determined for each segment and then averaged for that subject.

Statistical Analysis

Normality of data was tested using the Kolmogorov–Smirnov test. Continuous data are presented either as mean±SD or, where highly skewed, as median (first and third quartiles). Categorical data are presented as numbers (percentages). The χ² test or Fisher exact test was used to compare dichotomous data. The unpaired Student t test (when normally distributed) or Mann–Whitney U test (for non-normal data) was used to compare continuous variables between subjects with HIV infection and controls, as appropriate. Segmental data were averaged on a per-subject basis to control for clustering of segments within each subject. Post hoc Bonferroni correction was used to explore whether there were differences between the HIV-infected individuals on ART, HIV-infected individuals not on ART (n=13), and the HIV-uninfected controls (n=92). Bivariate correlations were assessed using the Pearson r or Spearman rs coefficient, as appropriate. All statistical tests were 2-tailed, and a P value of <0.05 was considered statistically significant. All analysis was performed using SPSS version 20 (IBM, Armonk, New York).

Results

Baseline Characteristics

Subjects with HIV infection were well matched with controls for age, sex, and comorbidities (Table 1); although in keeping with previous reports,18 there were more smokers in subjects with HIV infection (40% versus 12% of controls; P<0.005). Subjects with HIV infection had higher median serum levels of high-sensitivity C-reactive protein (3 [2–6] versus 1 [0–1] mg/L in controls; P<0.005). Of subjects with HIV infection receiving ART, 68% were on non-nucleoside reverse-transcription inhibitor–based regimen and 32% were on a protease inhibitor–based regimen.
LV Structure and Function

Compared with controls, there was no difference in LV end-diastolic volumes in subjects with HIV (78±14 versus 76±14 mL/m²; P=0.39) but 14% larger end-systolic volumes (22±7 versus 25±8 mL/m²; P=0.02) and 7% larger indexed LV mass (54±11 versus 58±11 g/m²; P=0.02; Table 2). Furthermore, there was a modest impairment in peak systolic circumferential strain in subjects with HIV infection (−17.5±2% versus −18.9±1.5% in controls; P<0.001), whereas diastolic circumferential strain rate was more profound being 29% lower in subjects with HIV infection compared with control subjects (71.5±19 versus 101±28 s⁻¹; P<0.001).

When comparing subjects with HIV infection on ART and those who were ART naive, there was no difference in LV end-diastolic or end-systolic volumes; although while still in the normal range, ejection fraction was an average 6% lower in those untreated (68±6% versus 64±9% in the treated HIV group; P=0.02; Table 3). There was no difference in LV mass or size, peak systolic circumferential strain, and diastolic circumferential strain rate between treated versus untreated subjects with HIV infection (Table 3).

Table 1. Baseline Characteristics of the Study Participants

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n=92)</th>
<th>HIV-Infected Subjects (n=103)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44±10</td>
<td>45±10</td>
<td>0.93</td>
</tr>
<tr>
<td>Men (n)</td>
<td>53</td>
<td>79</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25±4</td>
<td>26±4</td>
<td>0.13</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>12</td>
<td>40</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>14</td>
<td>5</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>1</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>14</td>
<td>11</td>
<td>0.57</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>1 (0–1)</td>
<td>3 (2–6)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Continuous data are mean±SD or median (first and third quartiles) unless otherwise indicated. BMI indicates body mass index; and hs-CRP, high-sensitivity C-reactive protein.

Tissue Characteristics

On T2-weighted STIR imaging, in subjects with HIV, there was a higher signal intensity ratio compared with controls (1.55±0.23 versus 1.49±0.13; P=0.02; Table 2; Figure 1). When assessing myocardial regions of injury on T2-weighted imaging using a threshold of a volume fraction of >40 mm², the median volume fraction was significantly greater in the HIV group versus controls 0.07 (0.10–0.19) versus 0.00 (0.00–0.06); P=0.01 (Table 2). There were higher native T1 values in subjects with HIV infection (969±28 versus 956±24 ms in controls; P=0.01; Table 2; Figure 2). When using a threshold of T1>990 ms, median values were significantly greater in subjects with HIV versus controls (0.06 [0.02–0.13] versus 0.03 [0.00–0.05]; P<0.001). There were no differences between ART-treated versus ART-untreated subjects with HIV (Table 3) when using STIR or T1-mapping tissue techniques.

Pericardial Effusions

Small pericardial effusions, usually less than a centimeter in maximal diameter, were found more frequently in subjects with HIV infection compared with control subjects (57% in the HIV group versus 21% in controls; P<0.001) as shown in Table 2. In subjects with HIV infection who

Table 2. Cardiovascular Magnetic Resonance Findings

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects (n=92)</th>
<th>HIV-Infected Subjects (n=103)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV indexed, mL/m²</td>
<td>78±14</td>
<td>76±14</td>
<td>0.39</td>
</tr>
<tr>
<td>LVESV indexed, mL/m²</td>
<td>22±7</td>
<td>25±8</td>
<td>0.02</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>72±5</td>
<td>66±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass indexed, g/m²</td>
<td>54±11</td>
<td>58±11</td>
<td>0.02</td>
</tr>
<tr>
<td>LA size, mm</td>
<td>31±4</td>
<td>28±3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mid SA circumferential strain, %</td>
<td>−18.9±1.5</td>
<td>−17.5±2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak diastolic circumferential strain rate, s⁻¹</td>
<td>101±28</td>
<td>71.5±19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>STIR T2 ratio</td>
<td>1.49±0.13</td>
<td>1.55±0.23</td>
<td>0.02</td>
</tr>
<tr>
<td>Volume fraction of STIR T2 area, &gt;40 mm²*</td>
<td>0.00 (0.00–0.06)</td>
<td>0.07 (0.01–0.19)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Proportion of patients with volume fraction of STIR T2 area, &gt;40 mm²</td>
<td>4 (0–5)</td>
<td>12 (4–17)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Native T1, ms</td>
<td>956±24</td>
<td>969±28</td>
<td>0.01</td>
</tr>
<tr>
<td>Volume fraction of T1, &gt;990 ms*</td>
<td>0.03 (0.00–0.05)</td>
<td>0.06 (0.02–0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proportion of patients with volume fraction of T1, &gt;990 ms</td>
<td>3 (1–5)</td>
<td>9 (4–11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of pericardial effusion, n (%)</td>
<td>19 (21)</td>
<td>58 (57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of LGE, n (%)</td>
<td>15 (16)</td>
<td>84 (83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume fraction of LGE, &gt;2SD (%)</td>
<td>1 (0–1)</td>
<td>3 (2–5)</td>
<td>...</td>
</tr>
</tbody>
</table>

Continuous data are presented as mean±SD or median (first and third quartiles) unless otherwise indicated. LGE indicates late-gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; SA, short axis; and STIR, short-tau inversion recovery.

*Median, 25th to 75th interquartile ranges.
were ART naive, the incidence of pericardial effusions increased to 77%; however, this was not statistically significant (Table 3; \( P = 0.13 \)).

**Patchy Fibrosis (LGE Imaging)**

As previously reported by our group,\(^9\) the presence of LGE was found more commonly in subjects with HIV infection compared with controls (83% versus 16%, respectively; \( P < 0.001 \)). Most HIV-infected subjects had small areas of non-ischemic midwall enhancement found most commonly in the basal inferolateral and lateral walls and in the basal to mid septum (Figure 3). Quantitative analysis of LGE revealed that subjects with HIV infection had overall a small volume of scarring (≈3% of total LV mass).

There was no difference in the proportion of LGE between treated versus untreated subjects with HIV infection (Table 3).

**Functional Correlates of LV Function in HIV-Infected Subjects**

In HIV-infected subjects, LV ejection fraction (LVEF) correlated modestly with both peak systolic strain (\( r = -0.39; P < 0.001 \)) and peak diastolic strain rate (\( r = 0.29; P < 0.001 \)) as expected. Interestingly, there was a modest negative correlation between LVEF and CD4 count nadir (\( r = -0.23; P = 0.03 \)).

**Table 3. Cardiovascular Magnetic Resonance Characteristics of Treated vs Untreated HIV**

<table>
<thead>
<tr>
<th></th>
<th>Subjects With HIV on ART (n=90)</th>
<th>Subjects With HIV and ART naïve (n=13)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV indexed, mL/m²</td>
<td>76±13</td>
<td>81±16</td>
<td>0.26</td>
</tr>
<tr>
<td>LVESV indexed, mL/m²</td>
<td>24±7</td>
<td>28±14</td>
<td>0.08</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>68±6</td>
<td>64±9</td>
<td>0.02</td>
</tr>
<tr>
<td>LV mass indexed, g/m²</td>
<td>58±110</td>
<td>61±18</td>
<td>0.28</td>
</tr>
<tr>
<td>LA size, mm</td>
<td>32±5</td>
<td>30±5</td>
<td>0.24</td>
</tr>
<tr>
<td>Mid SA circumferential strain, %</td>
<td>-17.5±3.0</td>
<td>-17.6±2.0</td>
<td>0.81</td>
</tr>
<tr>
<td>Peak diastolic circumferential strain rate, s(^{-1})</td>
<td>71±19</td>
<td>74±20</td>
<td>0.62</td>
</tr>
<tr>
<td>STIR T2 ratio</td>
<td>1.6±0.2</td>
<td>1.5±0.2</td>
<td>0.76</td>
</tr>
<tr>
<td>Volume fraction of STIR T2 area, &gt;40 mm² (%)</td>
<td>12 (7–15)</td>
<td>9 (6–13)</td>
<td>0.47</td>
</tr>
<tr>
<td>Native T1, ms</td>
<td>968±29</td>
<td>978±24</td>
<td>0.23</td>
</tr>
<tr>
<td>Volume fraction of T1, &gt;990 ms (%)</td>
<td>8 (6–15)</td>
<td>11 (5–23)</td>
<td>0.29</td>
</tr>
<tr>
<td>Presence of pericardial effusion, n (%)</td>
<td>49 (54)</td>
<td>10 (77)</td>
<td>0.13</td>
</tr>
<tr>
<td>Presence of LGE, n (%)</td>
<td>74 (82)</td>
<td>11 (85)</td>
<td>0.83</td>
</tr>
<tr>
<td>Volume fraction of LGE, &gt;2SD (%)</td>
<td>3 (2–4)</td>
<td>3 (2–5)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Continuous data are presented as mean±SD or median (first and third quartiles) unless otherwise indicated. LGE indicates late-gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; SA, short axis; and STIR, short-tau inversion recovery.

**Figure 1.** Areas of myocardial injury in HIV infection and controls evaluated by T2 (short-tau inversion recovery [STIR]) SI ratio demonstrating a greater proportion of patients with myocardial injury, in patients with HIV, compared with control subjects (\( P < 0.01 \)). SI indicates signal intensity.

**Figure 2.** Areas of myocardial injury in HIV infection and controls, as evaluated by native T1 values demonstrating a greater proportion of patients with HIV with myocardial injury compared with control subjects (\( P < 0.001 \)).
However, there was no association between strain or strain rate and HIV disease duration, viral load, CD4 nadir, or CD4 count on imaging. When comparing protease inhibitor versus non-nucleoside reverse-transcription inhibitor–based treatments, there is no difference in LV volumes, systolic function, strain measurements, STIR T2 signal intensity ratio and native T1 values, and the presence of pericardial effusions.

Discussion

We have demonstrated that in a contemporary cohort of asymptomatic individuals with treated HIV infection, there are changes in myocardial tissue characterization, which accompany alterations in myocardial structure and function. Treated HIV infection is associated with chronic inflammatory changes, including elevated inflammatory markers, and we now find evidence of chronic subclinical myocardial edema and fibrosis and a high incidence of pericardial effusions. We propose that these chronic systemic inflammatory changes may partly underlie the changes in cardiac structure, function, and high incidence of myocardial fibrosis seen in treated HIV patients.

In keeping with previous reports, we have demonstrated alterations in systolic and diastolic functions in asymptomatic subjects with HIV compared with control subjects. Our study has shown a modest reduction in LVEF (which was related to nadir CD4 count) and an increase in LV mass in subjects with HIV compared with control subjects. Increases in LV mass and LV hypertrophy are independent prognostic factors in the general population. We show reduced LVEF and elevated mass in subjects with HIV, which may be related to the increased cardiac morbidity and mortality in the population with HIV infection. The changes in LV mass were independent of hypertension and body mass index. Although the cause of these structural changes remains unclear, we propose that they are related to the subclinical edema observed. In keeping with this hypothesis, patients with rheumatoid arthritis, another chronic inflammatory disease, have increases in LV mass and reduced cardiac systolic and diastolic function, which are associated with disease duration. In keeping with an ongoing chronic inflammatory state, subjects with HIV infection had higher C-reactive protein values, increased pericardial effusions, and altered native myocardial T1- and T2-weighted signal intensity ratio, suggesting subclinical low-grade persistent inflammation.

Increases in native T1 mapping, as a quantitative measure of water content using CMR, although nonspecific, can be seen in acute myocardial edema, infarction, myocarditis, amyloidosis, and focal and diffuse fibrosis. We postulate that increased T1 represents a combination of patchy myocardial edema, fibrosis, and inflammation. The effect of this subclinical inflammatory process is unclear; however, given that our study demonstrates changes in myocardial function, we propose that this subclinical inflammation is a major mechanism, and as infection is a lifelong chronic condition, this inflammatory damage may be cumulative.

Before the era of ART, the most common cardiac manifestation of HIV infection was pericardial effusions and the survival of AIDS patients with effusions was significantly shorter (38% at 6 months) compared with those without pericardial effusions (93% at 6 months). With the introduction of ART, there was a marked reduction in their incidence. The Cardiovascular Diseases in HIV-related Subjects (HIV-Heart Study) investigated 802 patients with HIV, 85% of whom were on ART, and found echocardiographic evidence of pericardial effusions in only 2 patients. Our study, using comprehensive CMR, has shown a pericardial effusion incidence of...
58% in subjects on ART and 77% in those who were ART naive. The higher sensitivity of CMR has enabled demonstration of small pericardial effusions; and although these are not hemodynamically significant, they likely support the presence a low-grade inflammatory state.

As previously reported, we found small volumes of focal myocardial fibrosis, detected by LGE, in asymptomatic HIV-infected subjects. Historic studies have shown that at autopsy, 40% of HIV-infected patients had histological evidence of interstitial fibrosis although there has been a dearth of studies of myocardial fibrosis in contemporaneous cohorts of HIV-infected individuals. Even in the era of ART, with suppression of viral replication, treated HIV infection is associated with persistent inflammation, tissue fibrosis, suboptimal immune recovery, and organ damage. Given the frequent finding of myocardial fibrosis in inflammatory disease, such as seen after myocarditis, for instance, it is plausible that the frequent finding of fibrosis in HIV is secondary to chronic inflammation. Myocardial fibrosis in animal and human studies is associated with worsening ventricular systolic function, abnormal cardiac remodeling, and increased ventricular stiffness. We postulate the chronic myocardial inflammation leads to fibrosis, which may underlie the altered myocardial function in this group.

The cause of this chronic inflammatory milieu leading to myocardial edema, fibrosis, and pericardial effusions is unclear in the era of viral suppression. The inflammatory changes we describe may not be specific to HIV and could be a generalized response to any chronic systemic inflammatory disorder. Our data suggest that despite virological suppression, there is ongoing myocardial and pericardial inflammation in those with HIV infection. We have shown that subjects with treated HIV have higher systemic inflammation, with high levels of high-sensitivity C-reactive protein, compared with controls. Inflammatory cells are upregulated in cardiac myocytes in HIV infection and particularly cells that express CCR5—the coreceptor used by most transmitted HIV strains. CCR5 has been implicated in numerous CVDs, and in animal models drug targets to CCR5 has resulted in viral suppression with reduced cardiac dysfunction.

When comparing subjects with HIV who were on ART versus subjects who were treatment naive, despite the small numbers in the latter group, there were significant differences in LVEF between the 2 groups. We also noted that 10 of the 13 subjects not on ART showed evidence of pericardial effusions, suggesting that persistent viremia, leading to recruitment of inflammatory cells, may underlie these effusions. Given that we have also shown an association between CD4 nadir and LVEF, this further supports the rationale for early initiation of ART. Indeed, the World Health Organization has recently proposed that all patients with HIV be commenced on ART despite the CD4 count, and the recent results of the Strategic Timing of Antiretroviral Treatment (START) trial would support this proposition.

We think that our findings of increased myocardial edema and fibrosis provide a plausible mechanism for changes in cardiac function in patients with HIV. We do, however, note that the myocardial volumes, function, and tissue characteristic values are within the normal range in patients with HIV; so, our results are unlikely to directly affect individual patients with HIV. Whether these findings predispose to the development of cardiomyopathy or could explain subtle symptoms in patients with HIV is unclear.

Limitations
Our study has several limitations. First, native myocardial T1 values may increase with myocardial edema, fibrosis, infarction, myocarditis, or amyloidosis and are not specific for myocardial inflammation or fibrosis as discussed. Second, T2 mapping was not performed, which would have been an interesting comparison; however, T2 mapping at the present time seems to have a large interindividual variability, which may not have helped significantly in distinguishing between myocardial water from inflammation and that in an expanded extracellular space. Third, postcontrast T1 mapping and extracellular volume quantification were not performed. Fourth, besides T1 mapping, there is no other serum or histological test performed to support the presence of diffuse myocardial fibrosis in our patients; in this study of early myocardial disease in asymptomatic patients, no myocardial biopsy for histological correlations could be justified. Fifth, T2-weighted image analysis requires an increased signal intensity in myocardium relative to SI of skeletal muscle. In a systemic disease, that may also affect skeletal muscle, the magnitude of findings could be underestimated. Finally, patients with HIV but not on ART were limited in numbers although the proportion reflects current practice in the United Kingdom, making comparisons between the groups difficult. With a push toward early treatment for HIV, it is unlikely a large cohort of ART naive patients will be available for comparative studies to help determine the direct influence of ART on our findings.

Conclusions
Treated HIV is associated with chronic inflammatory changes, including chronic subclinical myocardial edema and a high incidence of pericardial effusions. These chronic inflammatory changes may underlie the high incidence of myocardial fibrosis and alteration in cardiac function observed in patients with treated HIV. Further studies are required to determine whether these inflammatory changes play a causal role in the increased cardiac morbidity and mortality in treated HIV and whether there is an additional need for anti-inflammatory therapy.

Acknowledgments
We gratefully acknowledge the role of infectious disease specialists and nurses in identifying patient patients for recruitment from the following hospitals: Churchill Hospital, Oxford; the Garden Clinic, Slough; Royal Berkshire Hospital, Reading; and the Orchard Clinic, Banbury.

Sources of Funding
Dr Holloway acknowledges the support from the Oxford National Institute for Health Research Biomedical Research Centre program and the Australian Heart Foundation. Dr Neubauer acknowledges support from the British Heart Foundation Centre of Research Excellence. The British Heart Foundation (FS07/030) supported
this work. This research was supported by the National Institute for Health Research Oxford Biomedical Research Centre based at the Oxford University Hospitals Trust at the University of Oxford.

Disclosures

Competing nonfinancial interests: US patent pending 61/387,591: SKP, MDR. Systems and methods for shortened look-locker inversion recovery cardiac gated mapping of T1; September 29, 2010. All rights sold exclusively to Siemens Medical. US patent pending 61/689,067: SKP. Color map design method for immediate assessment of the deviation from established normal population statistics and its application to cardiovascular T1-mapping images. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

With the advent of antiretroviral therapy, HIV has become a treatable condition, although with a higher prevalence of cardiovascular disease. The mechanisms of HIV-related heart disease, including myocardial dysfunction and fibrosis, are not well established. In a contemporary group of patients with treated HIV, we have demonstrated subclinical changes in cardiac structure, function, and tissue characterization, using cardiac magnetic resonance imaging. We think that our findings of increased myocardial edema and frequent pericardial effusions demonstrate ongoing cardiac inflammation despite effective antiretroviral treatment. We think that chronic inflammatory changes in the heart may underlie alterations in cardiac function and the higher prevalence of myocardial fibrosis in patients with HIV. Clinicians should be aware of the high proportion of pericardial effusions, subclinical edema, and myocardial fibrosis in patients with HIV undergoing clinical scans. Further studies are required to determine if early initiation of antiretroviral therapy will reduce the chronic cardiac inflammatory changes, subsequent dysfunction, and fibrosis in this group.
HIV-1–Related Cardiovascular Disease Is Associated With Chronic Inflammation, Frequent Pericardial Effusions, and Probable Myocardial Edema

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doi: 10.1161/CIRCIMAGING.115.004430

Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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