Myocardial inflammation and edema in People living with Human Immunodeficiency Virus

Running Title: HIV and early myocardium involvement revealed by CMR

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The burden of cardiovascular disease in people living with HIV (PLWH) has tripled over the last 20 years, with cardiac manifestations of disease ranging from coronary disease to heart failure (1). The pathophysiological mechanisms involved in the development of Human immunodeficiency virus (HIV) cardiomyopathy remain elusive. Subclinical structural and functional changes were demonstrated in PLWH, but studies that deployed advanced imaging techniques focused on patients already treated with anti-retroviral therapy (ART), potentially limiting the understanding of cardiac manifestations of HIV.

In this study, we evaluated myocardial changes in both treated and untreated PLWH by implementing advanced cardiac magnetic resonance (CMR) with tissue characterization by parametric mapping techniques in an upper-middle income country, Peru. Study participants were prospectively recruited an each provided, written informed consent. The study group consisted of 51 PLWH: 26 were receiving ART, 25 patients were treatment-naïve. Twenty-one healthy controls were selected by frequency matching. No patient had hepatitis C coinfection. Treatment-naïve patients were defined as newly diagnosed patients with HIV, with CMR performed either prior to or within 14 days of initiating ART. Of the ART treated group: 22 (85%) received both nucleoside (NRTIs) and non-nucleoside (NNRTI) reverse transcriptase inhibitors. The average time since the initial diagnosis of HIV was 5 ± 4.4 years. Undetectable viral load was defined as <40copies/ml. All scans were performed with a 3T MRI scanner (Prisma; Siemens). The protocol included cine imaging for volume and function assessment (strain analysis with feature tracking), Modified Look-Locker Inversion Recovery (MOLLI) T1 and T2 mapping. Gadoterate meglumine [0.1 mmol/kg] was administered for late enhancement (LGE) imaging and calculation of the extracellular volume fraction (ECV) was also performed. CMR readers were blinded to patients' category.

There were no significant differences in baseline characteristics and cardiac risk factors between patients and controls. Compared with controls, PLWH had reduced LV function: LVEF 61.4±4.1 vs 64.7±2.4%, p=0.001; Global longitudinal strain (GLS) -17.6±3.3 vs -21.0±3.8%, p=0.002. PLWH had increased native T1 (1294±20 vs 1230±9ms, p<0.001), T2 (41.5±2.4 vs 36.4±1.4ms, p<0.001) and global ECV (28.5±1.5 vs 24.8±0.9%; p<0.001). Amongst PLWH, 39% had LGE vs none of the controls (p<0.001), with the area of LGE being mid or subepicardial in the septal and inferolateral walls. Non-trivial pericardial effusions (≥5mm) were more common among PLWH compared to controls (29 vs 5%, p=0.004). Figure 1A

Untreated PLWH had higher global native T1 (1304±20 vs 1285±16ms; p<0.001) and ECV (29.3±0.7 vs 27.7±1.3%; p<0.001) compared to those on ART (Figure 1B). For PLWH, higher ECV was associated with a lower CD4 count, and this was independent of age, gender and LVEF (r=-0.46,p=0.001). Similarly, patients with a detectable viral load had higher ECV (29±1.1 vs 27.5±1.3, p<0.001) and higher native T1 (1300±21.2 vs 1286±16.8, p=0.02) than patients with an undetectable viral load. Figure 1C.

Consistent with previous studies (2, 3) this data supports a high prevalence of subclinical myocardial dysfunction and structural changes in PLWH. However, this is the first study that detected a significant expansion in ECV in PLWH, suggesting a greater myocardial impact of HIV than previously recognized, even in a young patient cohort (mean age 36). The elevation in T1 and T2 mapping values seen in PLWH is consistent with previous studies proposing myocardial inflammation as a component of the pathophysiological mechanism of HIV cardiomyopathy (4). Furthermore, these structural changes were more prominent in untreated patients (higher native T1 and ECV) compared to patients on ART, and ECV was higher in PLWH with lower CD4 count and higher viral load. These findings support the notion that ART treatment is likely to be offering a

protective myocardial effect. The presence of cardiac structural changes in PLWH, particularly the degree of ECV expansion raises several questions with regards to the optimal management of these patients, suggesting the need of prospective studies with serial cardiac evaluation.

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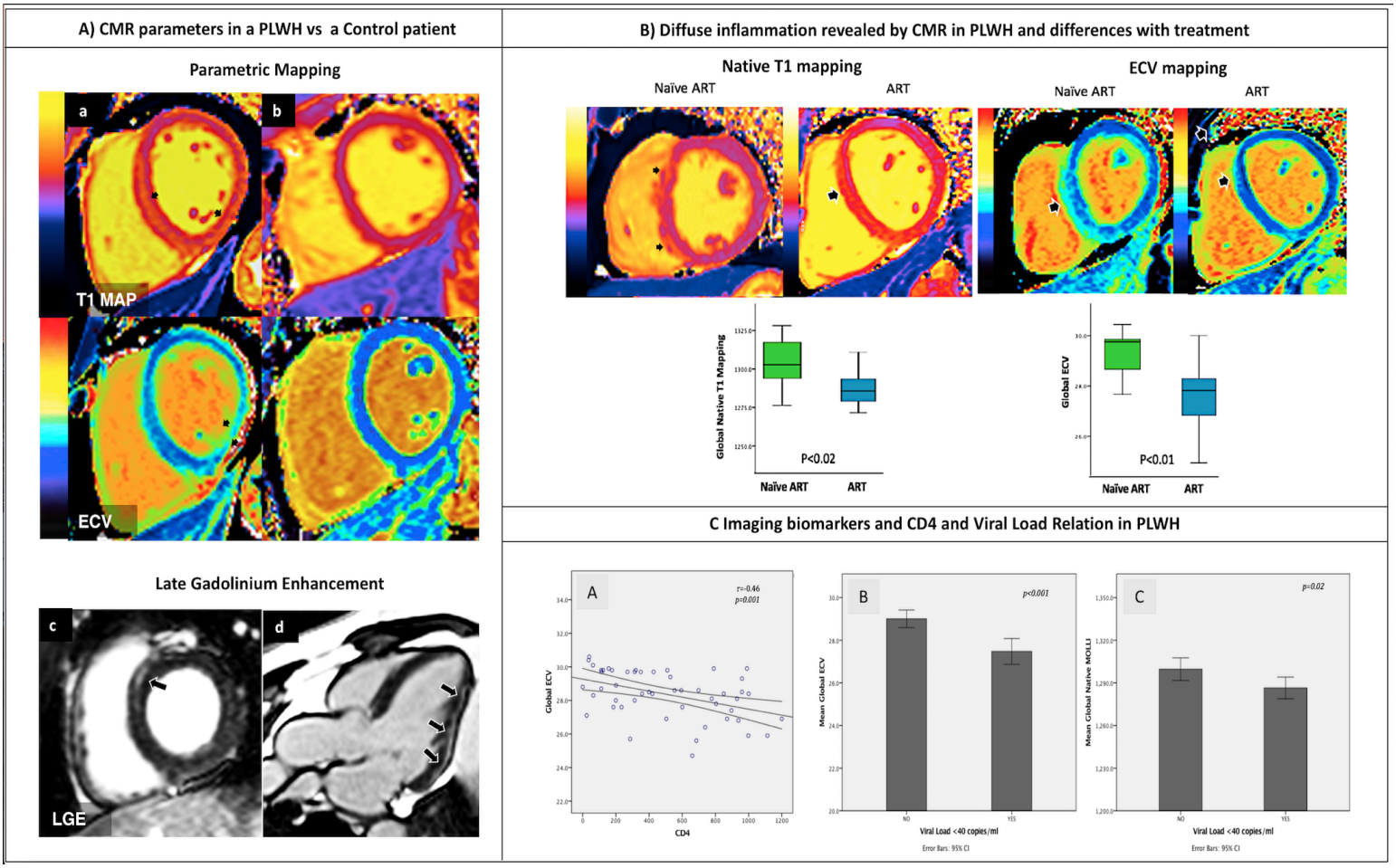

Figure 1A: CMR in a PLWH (a) and a control (b) showing increased native T1 mapping and ECV in PLWH **(c)** Basal antero-septal mid-wall and **(d)** Infero-lateral sub-epicardial LGE in PLWH. **Figure 1B:** ART-naïve PLWH have elevated native T1 and ECV compared to those on ART. **Figure 1C:** Inverse correlation between **(a)** ECV with CD4 total count, and **(b, c)** patients with a detectable viral load >40 copies/ml have higher global ECV and global native T1.