Myocardial Inflammatory Changes Before and After Antiretroviral Therapy Initiation in People With Advanced Human Immunodeficiency Virus Disease

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Because of the high frequency of late presentation of human immunodeficiency virus (HIV) disease in our population, we decided to explore the presence of myocarditis among people with HIV infection and advanced immunosuppression (less than 200 CD4$^+$ cells/µL) and to describe the inflammatory changes observed after combined antiretroviral therapy initiation in an observational, longitudinal, prospective cohort. We performed both cardiovascular magnetic resonance imaging and doppler transthoracic echocardiogram.

Keywords. antiretroviral therapy; HIV-associated myocarditis; IRIS; myocarditis.

Myocardial involvement in human immunodeficiency virus (HIV) infection has been described since the early years of the epidemic. The main conditions identified in these patients have been myocarditis, left ventricular dysfunction, and dilated cardiomyopathy [1–3]. These complications occur with increased frequency in people with advanced immunosuppression compared with those with higher CD4$^+$ cells count [4, 5]. Myocarditis is the most common cardiac histopathological

finding at autopsies of people dying of acquired immune deficiency syndrome (AIDS), with prevalences ranging from 30% to 52% [6–8].

The introduction of combined antiretroviral therapy (cART) initiation in developed countries resulted a reduction of 30% in the prevalence of HIV-associated cardiomyopathy and a shift in overall cardiac manifestations and HIV cardiovascular-related diseases [9, 10]. However, in developing countries, a high prevalence of HIV-associated myocardiopathy has mostly been associated with advanced immunosuppression [11, 12].

There are multiple factors responsible for HIV-associated myocarditis. Myocardial biopsy-based studies have confirmed an etiologic association with viral infections such as coxsackie virus group B, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) [9]. Other implicated organisms include *Toxoplasma gondii*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Aspergillu*s species, *Candida*, and *Mycobacterium avium intracellulare* [13]. In contrast, in some reports, it has not been possible to associate any pathogen, which suggests direct myocardial damage induced by HIV or a possible role of immune restoration disease [14–16]. The proportion of asymptomatic patients with HIV-associated myocarditis is still unknown [17].

Because of the high frequency of late presentation of HIV disease in our population, we aimed to explore the presence of clinical and subclinical myocarditis among people with HIV infection and advanced immunosuppression (less than 200 CD4$^+$ cells/µL) and to describe the inflammatory changes observed after cART initiation.

MATERIAL AND METHODS

Study Design

This is an observational, longitudinal, case study. The Ethics Committee on Human Subjects Research reviewed and approved the protocol and overviewed the study (reference INF-659). Patients were enrolled at the HIV/AIDS Clinic of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán in Mexico City between 2013 and 2016.

Study Population

We included adults, at least 18 years old, with HIV infection and advanced disease (CD4$^+$ T-cell counts <200 cells/µL), naive to cART. We excluded participants with previous or current cardiovascular disease, thyroid dysfunction, renal dysfunction defined as glomerular filtration rate of <90 mL/minute, use of injected drugs or cocaine 6 months before enrollment, previous use of anthracyclines, septic shock, ventilatory support, use of corticosteroids, claustrophobia, or gadolinium hypersensitivity.

Procedures

Participants were evaluated before and 6 weeks after cART initiation. All patients were assessed by a clinical cardiologist including physical examination. We performed cardiac imaging evaluation with cardiovascular magnetic resonance imaging (cMRI) and advanced techniques of doppler transthoracic echocardiogram (TTE) and 12 derivations electrocardiogram. We also measured troponin I and pro-b-type natriuretic peptide (NT-proBNP) as heart injury biomarkers, serum antibodies (enzyme-linked immunosorbent assay) for *T gondii*, *Trypanosoma cruzi*, EBV, CMV, and plasma polymerase chain reaction (PCR) for cardiotropic viruses including the following: human herpes virus (HHV)-6, HHV-8, coxsackie virus, and human parvovirus B19.

Cardiac imaging was performed with cMRI and doppler TTE before and 6 weeks after cART initiation. Myocardial inflammatory changes were determined based on Lake-Louis consensus criteria for myocarditis using a 1.5 T resonator (G.E. Twin; Medical Systems, Milwaukee, WI). The echocardiogram was performed by echocardiography specialists using G.E. Vivid 9 equipment. The cMRI findings were defined as consistent with myocardial inflammation if at least 2 of the following criteria were met: (1) regional or global myocardial signaling intensity increase in T2-weighted images; (2) increased global myocardial early gadolinium enhancement ratio between myocardial and skeletal muscle in gadolinium-enhanced T1-weighted images; (3) at least 1 focal lesion with nonischemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (late gadolinium enhancement) [18].

Echocardiogram systolic dysfunction was defined as a left ventricle ejection fraction (LVEF) <50%. All patients with diastolic dysfunction presented a slow relaxation pattern (E wave deceleration time >240 ms, E/A relation <1, E'/A' relation <1) [19].

The cMRI images were obtained and showed late reinforcement on short axis every 10 mm of the base at the apex, 2, 3, and 4 chambers; the cinema was made using the sequence steady-state free precession. The contrasted images were acquired on average 10–15 minutes after administration of contrast using the gradient-echo technique investment recovery, constantly adjusting the investment time for nullification of the normal myocardium. A 0.2 mmol/kg dose of gadolinium used dose. Titration was performed with heavy T2 (not contrasted), relative reinforcement; T1 heavy contrasted, global reinforcement. The images were interpreted by a specialist in cardiovascular imaging.

RESULTS

We enrolled 17 patients between 2013 and 2016. All patients voluntarily participated through an informed consent process. Baseline characteristics are summarized in Table 1. The cART

Table 1. Characteristics of 17 Patients With Advanced HIV-Associated Disease Before cART Initiation in Mexico (2013–2016)

Variable[a]	n (%)
Men	15 (88)
Age (years)	34 (IQR, 26–38)
CD4^{+} count (cells/μL)	46 cells/μL (IQR, 18–81)
AIDS-defining conditions	11 (65)
- Disseminated tuberculosis	4 (24)
- Chronic mucocutaneous herpes	3 (18)
- CMV esophagitis	1 (6)
- Cerebral toxoplasmosis	1 (6)
- Disseminated histoplasmosis	1 (6)
- Aseptic meningitis	1 (6)
Smoking	4 (24)

Abbreviations: AIDS, acquired immunodeficiency syndrome; cART, combined antiretroviral therapy; CMV, cytomegalovirus; HIV, human immunodeficiency virus; IQR, interquartile range.

[a]Continuous variables are shown using medians and 25th and 75th percentiles (referred as IQR). Binary variables are summarized using percentages.

regimens used were based on standard combinations according to local guidelines at the time.

Frequency of Myocardial Inflammation and Cardiac Dysfunction

We identified 9 patients with changes in cMRI suggestive of myocarditis (53%) at some point during the study. Six patients had myocarditis before cART initiation. Four patients shown resolution 6 weeks later and 2 patients had persistent myocardial inflammatory changes at 6 weeks. Three additional patients had no myocarditis at baseline and developed inflammatory changes 6 weeks after initiating cART (Table 2).

One of the patients with inflammatory changes in cMRI at baseline had systolic dysfunction (LVEF ≤50%) that persisted after 6 weeks and disappeared after 1 year of follow up. This patient was asymptomatic at baseline and developed clinically evident heart failure in the weeks after cART initiation.

In the 3 patients who developed myocarditis after cART initiation, there was no associated pathogen identified in the various assays performed (Figure 1). The mechanism involved is not understood, but the temporal association with cART initiation raises the possibility of immune restoration disease. CD4^{+} counts (cells/μL) were 106, 129, and 60 at baseline and increased to 225, 221, and 219 6 weeks after cART initiation. One year after cART initiation, 1 of the 3 had persistent myocardial inflammation in cMRI. At that time, those 3 patients had LVEF >50% measured by TTE.

As noted above, 2 patients with myocardial inflammation at baseline had persistent inflammatory changes 6 weeks after cART initiation. One of them developed clinically apparent heart failure characterized by dyspnea at rest, ankle edema, and jugular plethora. This patient also had disseminated *Mycobacterium bovis* infection. The LVEF at baseline was 41%, which improved with medical treatment (spironolactone, ivabradine, bisoprolol, and treatment of the infection). After

Table 2. Cardiac Imaging and Immunologic and Virologic Evaluation Before and Six Weeks After cART Initiation in 17 Patients With Advanced HIV-Associated Disease in Mexico (2013–2016) Using MRI and Transthoracic Echocardiogram

No.	Opportunistic Infections	CD4+ Cells/μL	HIV-RNA Copies/mL	Myocarditis on cMRI	LVEF	PASP	DD	PE	cART Scheme	Myocarditis on cMRI	LVEF	PASP	DD	PE	CD4+ Cells/μL	HIV RNA Copies/mL
1[a]	Chronic mucocutaneus herpes	106	355 785	-	64	5	-	-	TDF/FTC/EFV	+	60	22	-	-	225	1397
2	Cerebral toxoplasmosis	18	198 057	+	55	35	-	-	TDF/FTC/EFV	-	65	29	-	-	83	59
3[a]	None	129	599 388	-	58	30	-	-	TDF/FTC/EFV	+	64	35	-	-	221	502
4	Disseminated tuberculosis	5	1 942 375	-	69	34	-	-	TDF/FTC/EFV	-	72	5	-	-	93	209
5[a]	None	60	417 000	-	68	30	-	-	TDF/FTC/EFV	+	71	20	-	-	219	115
6	None	74	213 406	-	72	3	-	-	TDF/FTC/EFV	-	65	31	-	-	318	131
7[b]	Disseminated tuberculosis	88	949 063	+	41	20	-	-	TDF/FTC/EFV	+	50	33	SR	-	298	298
8	None	12	253 654	-	68	26	SR	-	TDF/FTC/EFV	-	73	30	-	-	56	69
9	None	46	777 620	-	56	28	SR	-	TDF/FTC/EFV	-	78	39	SR	-	197	87
10	None	25	2 144 996	+	72	24	-	-	TDF/FTC/EFV	-	74	29	-	-	208	2089
11	Chronic mucocutaneus herpes	36	726 855	-	65	20	-	-	TDF/FTC/EFV	-	73	33	SR	-	347	250 518
12	Chronic mucocutaneus herpes	81	505 172	+	70	8	-	-	TDF/FTC/EFV	+	70	7	-	-	298	108
13	CMV esophagitis	8	740 959	-	71	30	-	-	TDF/FTC/EFV	-	65	43	-	-	111	143
14	Disseminated tuberculosis	110	227 137	-	62	31	-	+	TDF/FTC + DOL	-	65	34	-	-	159	312
15	Aseptic meningitis	51	449 967	+	56	33	-	-	TDF/FTC/EFV	-	70	23	-	-	254	920
16	Disseminated histoplasmosis	7	129 924	-	67	30	-	+	TDF/FTC + RAL	-	54	20	-	-	27	40
17	Disseminated tuberculosis	34	125 840	+	65	48	-	+	TDF/FTC + RAL	-	56	33	-	-	20	40

Abbreviations: cART, combined antiretroviral therapy; cMRI, cardiovascular magnetic resonance imaging; DD, diastolic dysfunction; DOL, dolutegravir; EFV, efavirenz; FTC, emtricitabina; HIV, human immunodeficiency virus; LVEF, left ventricle ejection fraction; MRI, magnetic resonance imaging; PASP, pulmonary artery systolic pressure; PE, pericardial effusion; RAL, raltegravir; RNA, ribonucleic acid; SR, slow relaxation pattern; TDF, tenofovir.

[a]These patients developed myocardial inflammatory changes after cART initiation.

[b]This patient developed clinically significant heart failure requiring medical treatment for 1 year.
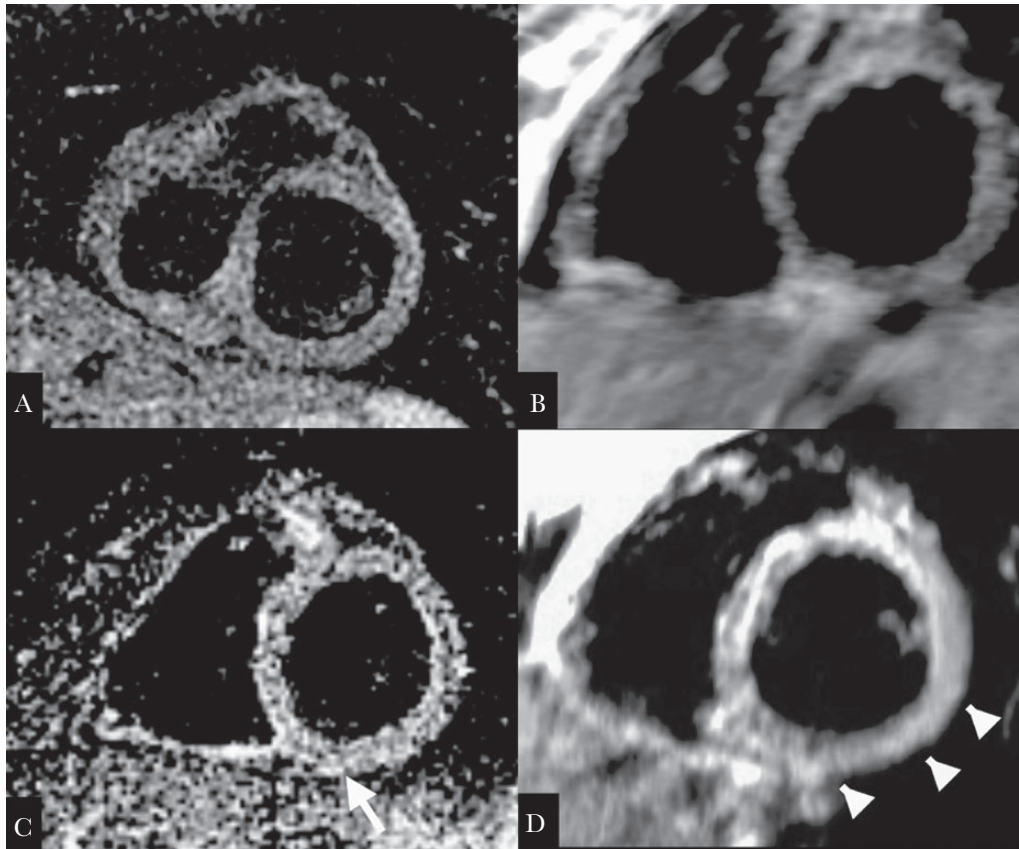
Figure 1. Cardiovascular magnetic resonance imaging of patient no. 3 (A and B). Baseline assessment shows normal postgadolinium short-axis sections: (A) T2W-STIR and (B) T1W. No images suggestive of myocarditis before combined antiretroviral therapy (cART) observed. (C and D) Six weeks after cART initiation; short-axis sections show myocardial inflammation. (C) T2W-STIR image with edema at inferolateral segment (white arrow). (D) T1W postcontrast image shows subepicardial enhancement in the same segment due to hyperemia (white arrow heads).

1 year of follow up, the LVEF was 61% measured by TTE, and the cMRI showed resolution of the inflammatory process. No patients had detectable heart injury biomarkers (troponin-I and NT-proBNP) at any time.

Screening of Pathogens

Immunoglobulin G serum antibodies for *T gondii*, CMV, and EBV were detected in 6, 16, and 17 patients, respectively, with no correlation with inflammatory changes. No patients had evidence of past or present *T cruzi* or coxsackie virus. We found no association between myocardial inflammation and serum PCR for any of these viral agents among patients who developed or had worsening myocarditis 6 weeks after cART initiation.

DISCUSSION

In this observational, descriptive study, we identified that approximately half of the patients with HIV and severe immunosuppression presented evidence of subclinical myocarditis on cMRI either before starting cART or 6 weeks after. Although this was a small group of patients, our observation suggests that subclinical myocarditis and asymptomatic cardiac dysfunction might be fairly common in people with advanced HIV-associated advanced disease. Although most of the patients improved after cART initiation, a minority developed myocardial inflammatory changes after therapy was initiated. Only one patient (see table 2) had clinical manifestations of myocarditis and myocardial dysfunction in the TTE.

In the absence of evidence of common etiological pathogens, development of myocardial inflammatory changes in cMRI after cART initiation may suggest either HIV associated or inflammatory disease associated with immune restoration as described previously. Moreover, 1 patient with baseline subclinical myocarditis and systolic dysfunction worsened during the first 6 weeks of cART and developed symptomatic heart failure in care, which is also consistent with paradoxical immune restoration disease. The long-term clinical relevance of asymptomatic myocarditis is unclear and deserves further evaluation.

A similar case of acute myocarditis with refractory ventricular arrhythmias in a patient with AIDS who experienced rapid immune recovery within the first weeks of cART initiation and considered to be caused by immune reconstitution inflammatory syndrome was reported in 2008 [20]. The development of

myocarditis in 3 patients or worsening of the condition in one after starting cART may represent a little-known presentation of immune restoration associated disease affecting the heart, which mostly fulfills criteria for this syndrome [21, 22].

CONCLUSIONS

To our knowledge, this is the first study that evaluates myocardial inflammatory changes using cMRI before and after cART initiation. Cardiovascular MRI has a high sensitivity to detect areas of inflammation or myocardial necrosis, which is why it is the preferred method for diagnosing acute myocarditis [23]. The main limitation of the study is the small group of patients evaluated in a single referral center, which may restrict the generalization of our findings to other settings. Our findings emphasize the need for further research on myocardial dysfunction and heart inflammatory diseases in people with advanced HIV disease. Awareness of these conditions may improve management of patients with advanced HIV infection.

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