Human Immunodeficiency Virus-Associated Rheumatic Disorders in the HAART Era

JAVIER MARQUEZ, CARLOS S. RESTREPO, LILIANA CANDIA, ALBERTO BERMAN, and LUIS R. ESPINOZA

ABSTRACT. ***Objective.*** To define the frequency and characteristics of human immunodeficiency virus (HIV)-associated rheumatic manifestations in patients receiving highly active antiretroviral therapy (HAART) referred to a rheumatology clinic.

Methods. A total of 75 patients with HIV infection receiving HAART were prospectively evaluated for the presence of rheumatic complaints. Diagnosis of HIV infection was performed by ELISA and confirmed by Western blot, and all HIV patients were classified according to the US Centers for Disease Control criteria.

Results. Seventy-five individuals with HIV infection and musculoskeletal manifestations were evaluated: 65 (86%) men and 10 (14%) women. Mean age was 32 ± 4.5 years (range 21–58). The group included 40 (53%) heterosexuals, 30 (40%) intravenous drugs users, 9 (12%) homosexuals, 3 (4%) who had received blood transfusion, and 2 (2.6%) with unknown risk factors. Septic manifestations were the most common complications seen in 31 (41%) out of 75, and included septic arthritis, cellulitis, osteomyelitis, diskitis, and pyomyositis. Fibromyalgia was present in 13 (17%), seronegative symmetric polyarthritis in 4, oligoarthritis in 4, psoriatic arthritis in 2, carpal tunnel syndrome in 2, and enthesitis in 2. Mutifocal bone non-Hodgkin's lymphoma was present in 7 (9.3%) and Kaposis's sarcoma of bone in 2 (2.6%) patients. Hypertrophic osteoarthropathy in 3 (4%) and aseptic bone necrosis of multiple bones was seen in 3 (4%) patients. Ten patients exhibited only arthralgias. Most patients had moderately elevated erythrocyte sedimentation rate and C-reactive protein. Mean CD4 cell count was 250 mm^3 (range 20–450), and mean HIV viral load was 5210 (range 0–75,300) copies/ml.

Conclusion. Rheumatic manifestations were highly frequent in HIV patients receiving HAART referred to a rheumatology clinic, although the clinical spectrum differed from the pre-HAART era with septic and malignant complications being the most common manifestations seen. (J Rheumatol 2004;31:741–6)

Key Indexing Terms:

HIV ARTHRITIS SEPTIC ARTHRITIS
TROPICAL PYOMYOSITIS HAART KAPOSI'S SARCOMA

The association between human immunodeficiency virus (HIV) infection and inflammatory musculoskeletal (MSK) disorders is well established[1-5]. A wide spectrum of rheumatic conditions, including reactive arthritis (ReA), psoriatic arthritis (PsA), ankylosing spondylitis, undifferentiated seronegative spondyloarthropathy, polymyositis, vasculitides, septic arthritis, pyomyositis, fibromyalgia, avascular necrosis, and more recently osteoporosis has been described in association with HIV infection[6,7]. The prevalence of these MSK manifestations varies greatly among the different studies, ranging from less than 1% to over 60%. This wide variability may be secondary to a number of factors including patient selection, ethnic background of the population under study, risk factors, stage of HIV infection, specific highly active antiretroviral therapy (HAART), and the design of the studies (prospective or retrospective) among others.

Regarding the latter, it should be stated that most investigations of the association between HIV and MSK involvement were undertaken prior to the advent of HAART.

The availability of HAART in the past several years has made a significant impact on the natural history, longterm prognosis, morbidity, and mortality of patients with HIV[8-10]. Whether this therapeutic modality affects the expression of rheumatic manifestation associated with HIV infection has not been fully explored. Berman, *et al*[11] attempted, unsuccessfully several years ago, to establish whether or not the use of antiretroviral therapy alters the frequency or expression of rheumatic manifestations in HIV infected individuals. Our objective was to determine the frequency and clinical expression of rheumatic manifestations in HIV-infected individuals receiving HAART.

From the Rheumatology Section, Departments of Medicine and Radiology, LSU Health Sciences Center, New Orleans, Louisiana, USA, and the University of Tucuman School of Medicine, Tucuman, Argentina.

J. Marquez, MD, Research Fellow; L, Candia, MD, Research Fellow; C. Santiago Restrepo, MD, Associate Professor; L.R. Espinoza, MD, Professor and Chief, Section of Rheumatology, Departments of Medicine and Radiology, LSU Health Sciences Center; A. Berman, MD, Professor, University of Tucuman School of Medicine.

Address reprint requests to Dr. L.R. Espinoza, LSU Medical Center, 1542 Tulane Avenue, New Orleans, LA, 70112-2822, USA.

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MATERIALS AND METHODS

A total of 75 individuals with HIV infection referred to our rheumatology clinic (LSU Health Sciences Center) were evaluated between April 1999 and March 2002. All patients had a complete history and physical examination, laboratory investigation [including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor, and antinuclear antibody (ANA)] and diagnostic imaging studies that included plain joint radiographs, computed tomography (CT) and magnetic resonance imaging (MRI) when necessary. Inclusion criteria for this study included: HIV-positivity by enzyme-linked immunosorbent assay (ELISA) confirmed by Western blot, treatment with HAART (defined as the use of 2 nucleoside reverse transcriptase inhibitors and 1 protease inhibitor and/or 1 non-nucleoside reverse transcriptase inhibitor), and diagnosis of a MSK disorder.

All patients were interviewed and complete rheumatologic evaluation was performed by one of us (LRE). Age, sex, risk factors for HIV infection, CD4 cell count (by flow cytometry and FACS scan; Becton Dickson), and HAART were characterized. Diagnoses of rheumatic disorders were made using established and/or ACR classification criteria.

RESULTS

Seventy-five individuals with HIV infection and MSK manifestation were evaluated: 65 (86%) men and 10 (14%) women. Mean age when first seen was 32 ± 4.5 years (range 21–58); mean disease duration 13.1 years (range 3–20). Risk factors for HIV infection included heterosexual transmission 40 (53%), intravenous drug use 30 (40%), homosexual transmission 9 (12%), blood transfusion 3 (4%), and unknown 2 (2.6%). All HIV patients received HAART, mean duration 2.3 years. Mean CD4 cell count was 250/mm^3 (range 20–450). Acquired immune deficiency syndrome (AIDS) was present in 40/75 (53.3%); the mean plasma viral load was 5210 (range 0–75,300) copies/ml.

There were no differences in CD4 cell count among subsets (according to risk factors) of HIV patients (Table 1).

MSK manifestations. All patients exhibited inflammatory and noninflammatory MSK involvement; septic complications were the most common clinical manifestations and were seen in 31 patients (41%). They included septic arthritis, septic bursitis (Figure 1), cellulitis, osteomyelitis, diskitis, and pyomyositis in 31 patients (41%) (Figure 2). Fibromyalgia was present in 13 out of 75 individuals (17%), seronegative symmetric polyarthritis in 4 (1 erosive and 3 non-erosive), oligoarthritis in 4 (5.3%), psoriatic arthritis in 2 (2.6%), rhabdomyolysis in 1, carpal tunnel syndrome in 2 (2.6%), and enthesitis in 2 (2.6%). Multifocal bone non-Hodgkin's lymphoma was present in 7 patients (9.3%) and Kaposi's sarcoma of bone was seen in 2 patients (2.6%) (Figures 3 and 4). Hypertrophic osteoarthropathy was present in 3 (4%) and aseptic bone necrosis of multiple bones was seen in 3 (4%) (Figure 5). Arthralgias alone were present in 10 patients (13%); several patients exhibited more than one rheumatic syndrome (Table 2). A total of 23 (32%) HIV individuals were febrile (temperature > 37.5ºC) at presentation. Most patients had mild to moderate elevation of ESR and CRP (data not shown) and rheumatoid factor and ANA testing were negative in the great majority (data not shown). Only 7 patients (9%) had leukocytosis at presentation (WBC > 11,000/ml). HIV positivity by ELISA and Western blot was confirmed in all patients.

Staphylococcus aureus was identified in 22/31 patients (71%) with septic complications, *Streptococcus pyogenes* in 1/31, *S. pneumoniae* in 1/31, *Mycobacterium tuberculosis* in 1/31, *Klebsiella pneumoniae* in 1/31, *Nocardia asteroides* in 1/31, *Salmonella* species in 1/31, *Cryptococcus neoformans* in 1/31, and 2/31 infections were of unknown etiology.

All HIV patients had been or were receiving HAART when first evaluated.

Table 1. Demographic characteristics of HIV patients.

Age, yrs ± SD	32 ± 4.5
Sex, male (%)	65 (86)
Disease duration, yrs ± SD	13.1 ± 6.4
Risk Factors n (%)	
Heterosexual transmission	40 (53)
IV drug abuse	30 (40)
Homosexual transmission	9 (12)
Blood transfusion	3 (4)
Unknown	2 (2.3)
Laboratory	
CD4 cell count, cells/ml ± SD	250 ± 173
Viral load, copies/ml ± SD	5210 ± 2970

DISCUSSION

Musculoskeletal involvement is a common complication of HIV infection, especially in Central Africa, but it has been reported from almost every part of the world[12-14]. Available reports, however, have clearly shown that there are definite geographic variations in terms of prevalence and clinical manifestations seen[5,15-17]. Most reports on the association of HIV infection and rheumatic disorders date from a period prior to the advent of HAART. The introduction of the latter therapeutic modality in the mid 1990s, as well as the use of prophylactic measures with antibiotics for the prevention of opportunistic infections, particularly *Pneumocystis carinii* pneumonia, led some investigators to think that this form of therapy may influence the natural history of rheumatic disease in the HIV infected population[8-10].

An early attempt to study the effect of antiretroviral therapy on the MSK manifestations of HIV infection failed to find any reduction on either the frequency and/or clinical expression of rheumatic manifestations associated with HIV. Berman, *et al*[11] studied 80 patients of whom 38 received antiretroviral therapy such as zidovudine, didanosine, and zalcitabine, alone or in combination, and a second group of 42 patients who received no treatment. At the end of the followup period of approximately 12 months (range 2–36) both groups exhibited the same clinical spectrum of inflammatory MSK manifestations. It should be added, however, that most patients only received one or 2 antiretroviral agents and only for a relatively short period of time.

Results from our study in a highly selected group of

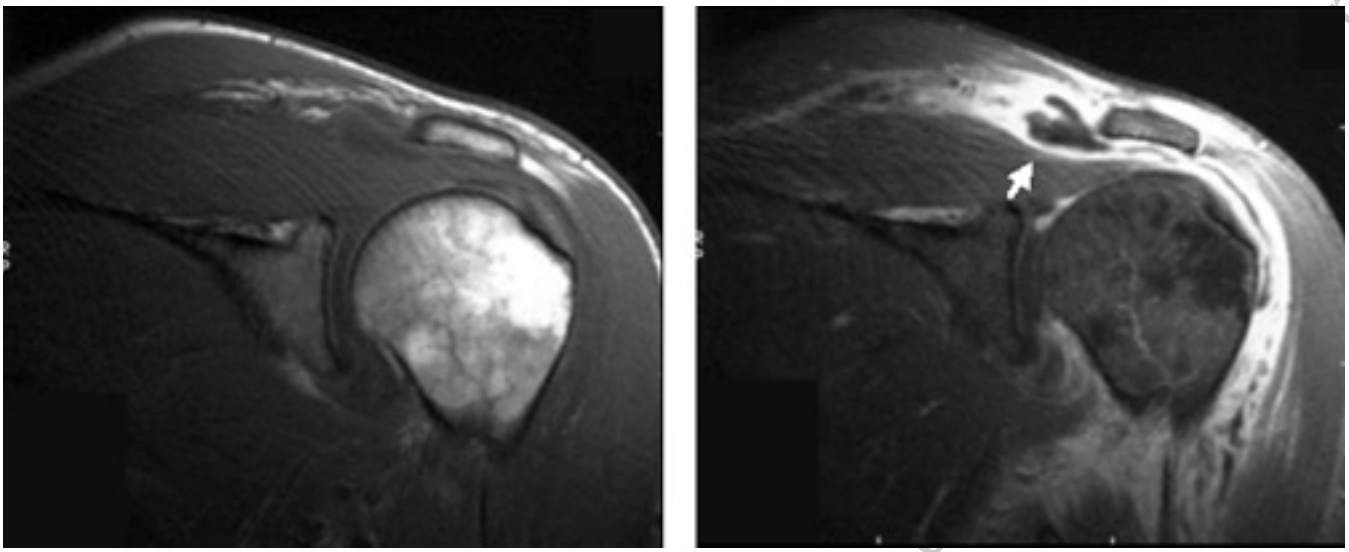

Figure 1. Twenty-eight-year-old man with fever and shoulder pain. Septic bursitis of the left shoulder. A. Oblique coronal T1-weighted image. B. Oblique coronal T1-weighted image with fat suppression after gadolinium injection. Fluid is seen within the subacromial-subdeltoid bursa, with peripheral enhancement of the synovial lining after contrast injection (arrow). Bone marrow appears normal on both sequences.

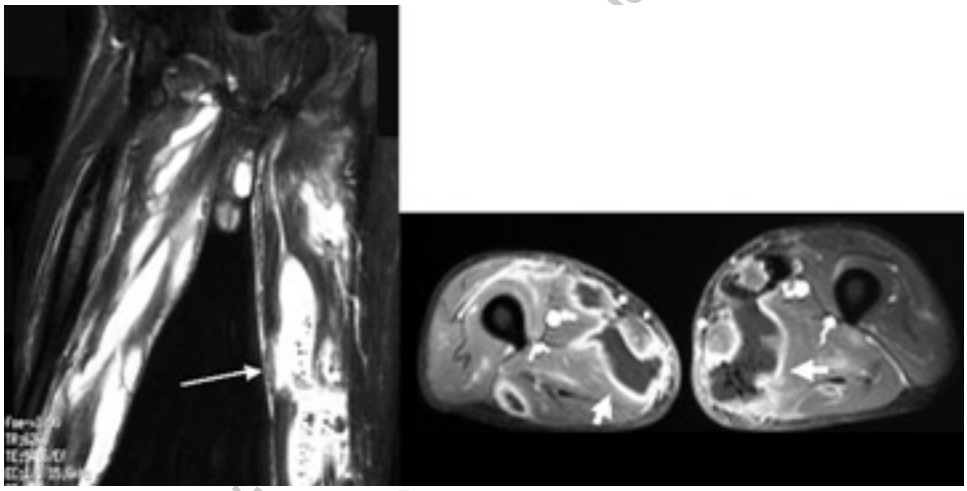

Figure 2. Thirty-one-year-old male intravenous drug user. Multiple soft tissue abscesses at the level of mid-thighs. A. Coronal T2-weighted image. B. Axial T1-weighted images after gadolinium. Soft tissue abscesses at the mid-thigh are visible. Gas within the fluid collection is visible (long white arrow). In the images after gadolinium injection there is rim enhancement in the periphery of the necrotic collections (short white arrow).

patients seem to indicate that MSK manifestations remain highly prevalent in HIV infection, but a definite shift in the clinical spectrum has occurred. An association, however, between clinical rheumatic manifestations with low CD4 cell count and high plasma viral load was observed; although there were no differences in CD4 cell count and viral load between HIV patients with septic complications and other clinical rheumatic disorders. It should be noted, however, that the relatively high HIV viral load seen in this population may indicate that the patients' HIV infection was not under strict control. Initial descriptions uniformly reported seronegative spondyloarthropathies including reactive arthritis, psoriatic arthritis, and undifferentiated spondyloarthropathy as the most common rheumatic disorders associated with HIV. Early descriptions also reported a very low incidence of osteoarticular septic complications in HIV patients from the Western world in whom homosexual behavior was the most common risk factor[1-4,18-22]. At variance with these findings were the Spanish reports describing osteoarticular infection, including septic arthritis and pyomyositis as the most common osteoarticular manifestations associated with HIV infection[16,17,21]. This difference was attributed to geographic differences and differences in risk factors with a high prevalence of intravenous drug use

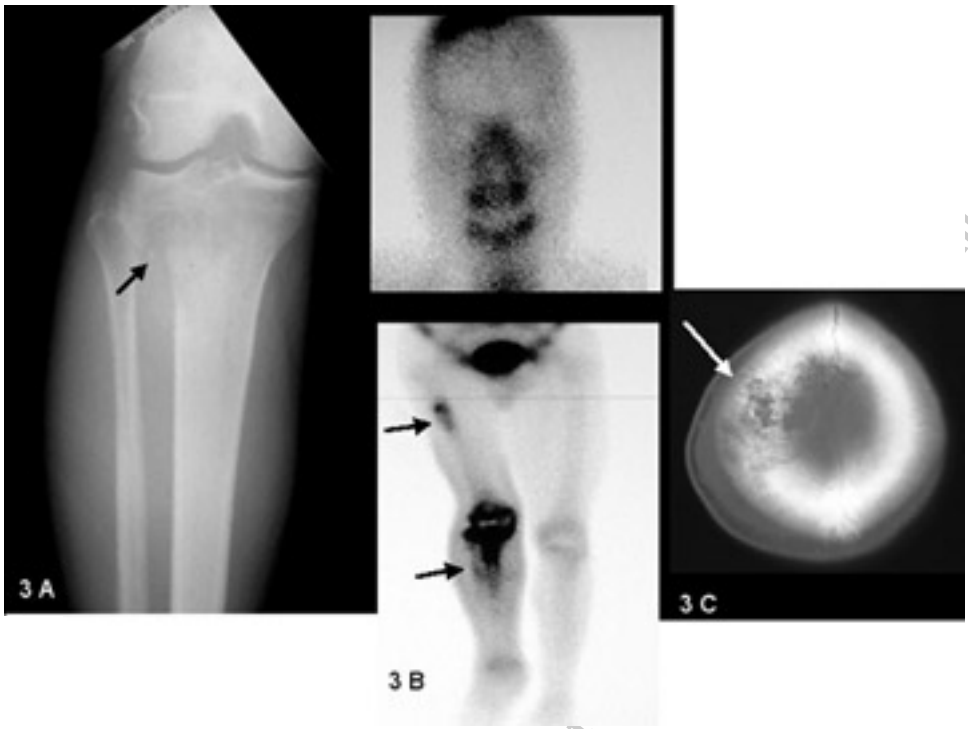

Figure 3. Twenty-six-year-old man with weight loss and fever. Multifocal bone non-Hodgkin's lymphoma. A. Right knee AP view. B. Bone scan. A poorly defined moth-eaten pattern is visible at the proximal metaphysis of the tibia. A lytic lesion with similar pattern is identified on the right parietal bone. Increased uptake in the skull, proximal shaft of the right femur, and right knee is clearly visible. C. CT of head. Bone window.

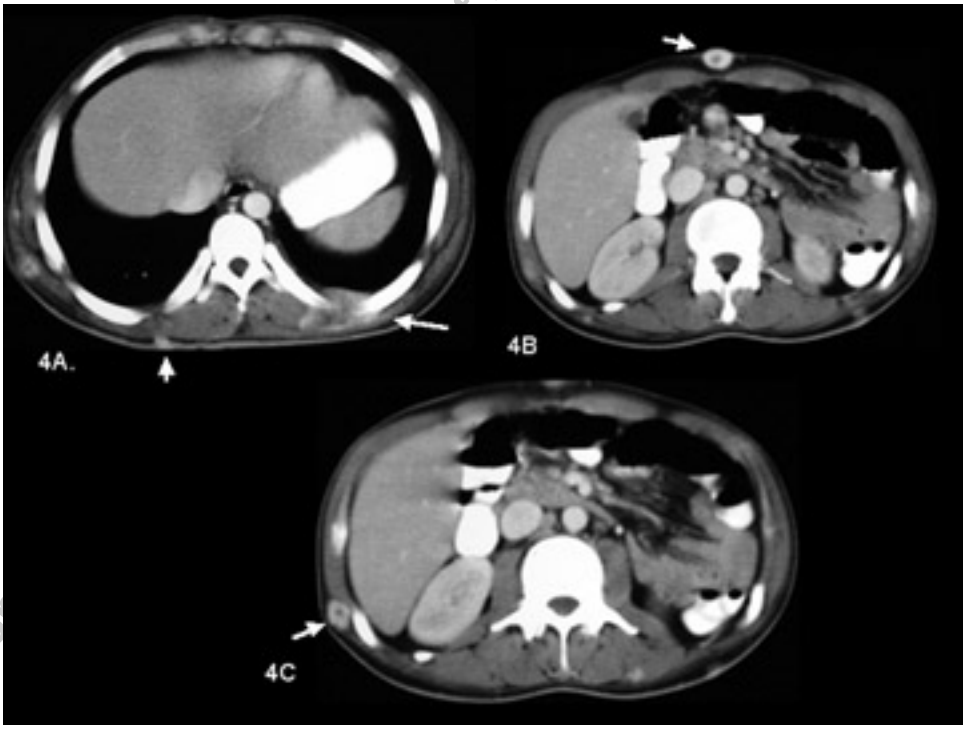

Figure 4. Thirty-five-year-old man with axillary lymphadenopathy and purple plaques on the skin. Kaposi's sarcoma. A, B, and C. Axial contrast CT of the abdomen. Multiple subcutaneous nodular lesions are visible at the posterior thoracoabdominal region and right lateral abdominal wall, all showing intense enhancement after contrast. One lesion reveals bone involvement; cortical erosion and destruction of posterior arch of the rib is seen (arrows).

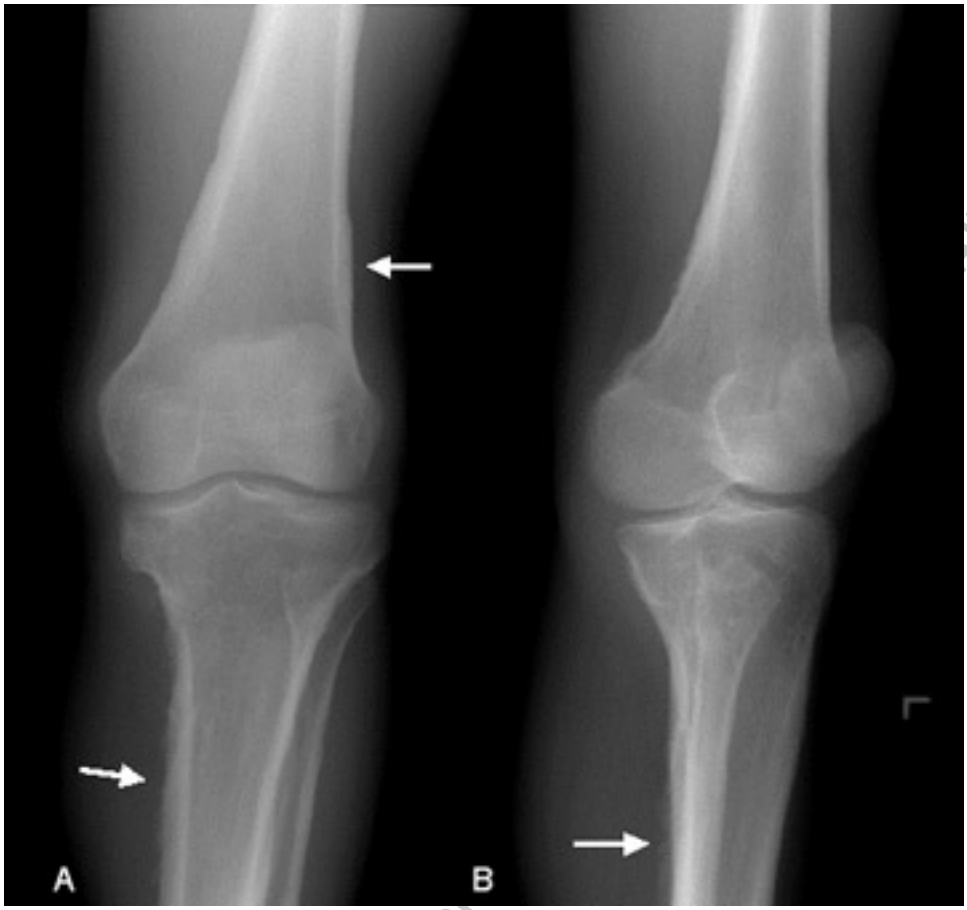

Figure 5. Thirty-nine-year-old man with long bone pain. Hypertrophic osteoarthropathy. A. Right knee, AP view. B. Lateral view. A laminar periosteal reaction is noted in the femoral, tibial, and fibular shaft. Articular alignment is preserved.

Table 2. HIV-associated rheumatic disorders in 75 patients.

Rheumatic Disorder	n (%)
Septic involvement	31 (41)
Septic arthritis	6 (8)
Septic bursitis	3 (4)
Cellulitis	2 (2.26)
Osteomyelitis	15 (20)
Diskitis	1 (1.3)
Pyomyositis	4 (5.3)
Bone and articular involvement	26 (34.6)
Arthralgias	10 (13)
Symmetric polyarthritis	4 (5.3)
Oligoarthritis	4 (5.3)
Osteonecrosis	3 (4)
Hypertrophic osteoarthropathy	3 (4)
Psoriatic arthritis	2 (2.6)
Neoplasm	9 (12)
Non-Hodgkin's lymphoma	7 (9.3)
Bone Kaposi's sarcoma	2 (2.6)
Miscellaneous	16 (21.3)
Fibromyalgia	13 (17)
Carpal tunnel syndrome	2 (2.6)
Rhabdomyolysis	1 (1.3)

in the Spanish series. Our report shows septic complications as the most common MSK manifestations, and also shows a high frequency of bone malignancy which has not been previously seen except in a recent report from Spain[21]. Of interest spondyloarthropathy was still seen, but at a much lower frequency.

A number of factors, in addition to the low CD4 cell count, may have played a role in our findings, especially the higher frequency of IV drug use and heterosexual transmission as risk factors noted in our study. A similar high incidence of septic complications in HIV individuals with low CD4 cell count and risk factors had been reported[15,19]. Of interest, most of the seronegative spondyloarthritis and polyarthritis noted in the present series was seen among homosexuals, and this has been described in other series[16,21]. Factors such as longer survival time and/or high rate of AIDS among our patient population and the use of HAART may have also influenced the clinical expression in our patient population. Other investigators have also described an increase in non-HIV related cancer following HAART in HIV, and consideration should also be given to some of the side effects associated with this therapeutic modality

including metabolic and inflammatory articular disorders[23–25].

It can be concluded that despite HAART, musculoskeletal manifestations remain relatively common in HIV infected individuals although the clinical spectrum of HIV-associated rheumatic disease has changed, with septic and malignant involvement being the most common manifestations noted.

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