Rheumatic manifestations in HIV-1 infected in-patients and literature review

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Abstract

Objective
To report the rate and spectrum of the rheumatic manifestations of human immunodeficiency virus (HIV) since the advent of highly active anti-retroviral therapy (HAART).

Methods
A retrospective record review of 888 inpatients with HIV for rheumatic manifestations was performed from January 1995 to March 2006. We then searched the 888 records for rheumatic diseases using International Classification Diagnostic (ICD) Codes. The medical records of the cases of HIV with the rheumatic conditions were then reviewed. A computer-assisted search of Medline/Pubmed for the medical literature from January 1981 to August 2007 using the keywords HIV, acquired immune-deficiency syndrome, rheumatic manifestations, combining with text words like systemic lupus erythematosus (SLE). Only English language literature was included.

Results
The demographic data of 888 cases of HIV included men (64%) and women (36%) with a mean age of 41.5±10.2 years. Race consisted of Black (70%), White (22.8%), Hispanic (6.5%), and others (1.1%). Rheumatic manifestations were present in 80 (9%) with arthritis/arthralgia 49 (5.5%), septic arthritis 9 (1%), and osteomyelitis 8 (0.9%), connective tissue diseases (CTDs) 6 (0.7%) (SLE 3, rheumatoid arthritis 1, polymyositis 1, and systemic sclerosis 1), avascular necrosis 6 (0.7%) (hips 3, knees 2, and shoulder 1). There were no cases of seronegative spondyloarthritis or Sjögren’s syndrome.

Conclusions
There was an association of HIV with rheumatic conditions in 9%, including CTDs and avascular necrosis. In addition, there were no cases of the seronegative spondyloarthritis subsets. This change in spectrum from prior reports suggests the rheumatic manifestations of HIV have changed, perhaps related to HAART.

Key words
Rheumatic manifestation, HIV, AIDS, connective tissue disease, systemic lupus erythematosus, osteonecrosis.
Introduction

Human immunodeficiency virus (HIV) may present as a spectrum of disease from primary HIV infection to acquired immunodeficiency syndrome (AIDS), the latter being defined as CD4 cell count below 200/mm³ regardless of the presence or absence of symptoms (1). Since the description of HIV (2) and AIDS (3) in 1981, there have been reports of a variety of associated rheumatic disorders (4). However, much of the published literature on the rheumatic manifestations of HIV/AIDS predated the highly active anti-retroviral therapy (HAART) era (5-7). It has been suggested (8) that the spectrum of rheumatic disorders associated with HIV/AIDS may have changed because of HAART. To re-examine the prevalence and patterns of rheumatic manifestations of HIV, we reviewed the rheumatic diseases in 888 hospitalized HIV/AIDS patients between 1995 and 2006 since few cases of HIV inpatients were documented before 1995.

Methods

The computerized database of medical records of patients with HIV/AIDS hospitalized at Fuld Campus, Capital Health System (a community hospital) from January 1995 to March 2006 was searched using International Classification Diagnostic (ICD) discharge codes. The diagnosis of HIV/AIDS was primarily made by subspecialists in infectious disease and confirmed by ELISA and western blot. Information contained in the database included name, sex, age, and race on each case of HIV/AIDS as well as codes of additional discharge diagnoses. We then searched for combinations of HIV/AIDS with any of the following rheumatic diseases using corresponding ICD codes: arthralgia, arthritis, reactive arthritis (Reiter syndrome), psoriasis, psoriatic arthritis, ankylosing spondylitis, septic arthritis, osteomyelitis, osteonecrosis or avascular necrosis (AVN), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), polymyositis (PM), dermatomyositis, scleroderma (SSc), and Sjögren’s syndrome (SS).

The medical records of the cases of HIV/AIDS with the above rheumatic conditions were reviewed for confirmation of their rheumatic manifestations, relevant laboratory findings, and imaging studies as well as HIV/AIDS risk factors, pharmacological treatment and HIV’s relationship to a particular rheumatic disease. There were 888 cases of HIV/AIDS admitted to the hospital in the 11 years of the study (Table I). Descriptive statistics were tabulated as frequency and percentage of rheumatic manifestations.

A computer-assisted search of Medline/Pubmed for the medical literature spanning from January, 1981 to August 2007 using the keywords: HIV, AIDS, rheumatic manifestations, combining with text words like SLE, RA, SSc, PM, SS, AVN, spondyloarthritis, arthritis/arthritis, and skeletal infection, in the English language literature with pertinent information was included.

Results

There were 80/888 (9%) patients with rheumatic findings (Table II).

Connective tissue diseases (CTDs)

SLE

There were 3 women with SLE. All had the diagnosis of SLE prior to the confirmation of HIV. Two fulfilled American College of Rheumatology (ACR) classification criteria and case no. 3 had 3 of the classification criteria.

Case no. 1: SLE

A 55-year-old white woman was documented to have SLE with several hospital admissions between 1985 and 1993. At that time, she had anemia, proteinuria, renal insufficiency, positive antinuclear antibody (ANA) 1:320, anti-dsDNA antibody 640 (normal range <30) IU/ml and CH50 50 (normal 60-144) CAE U/ml, C₃ 47 (normal 71-141) mg/dl, and C₄ 14 (normal 12-34) mg/dl documented in 1993. This patient was diagnosed in 1991 as having a positive HIV test 6 years after the diagnosis of SLE. No risk factor for HIV was found in the medical records. Persistent proteinuria and renal insufficiency in 1995 resulted in a renal biopsy reported as inactive lupus nephritis with World Health Organization (WHO) class III. Prior to the diagnosis of HIV, flares
of her SLE and slowly progressive renal failure resulted in hemodialysis by 1996. On follow-up, the patient was maintained on prednisone (less than 20 mg/day). She was off HAART due to a poor compliance. As of January 2006 her CD4+ lymphocyte count was 395 cells/μl.

Case no. 2: SLE
A 26-year-old Hispanic woman was documented to have polyarthritis, pancytopenia, proteinuria, microscopic hematuria and positive ANA (titer 1:80, homogeneous) with a diagnosis of SLE prior to 1994. This resulted in end stage renal disease (ESRD) in 1998. She was then found to have heterosexually transmitted HIV in 1994, her husband having had HIV/AIDS. The patient was lost to follow-up.

Case no. 3: SLE
A 23-year-old African American woman was recorded in 2002 to have a left pleural effusion on chest radiograph, pancytopenia, and proteinuria (3 classification criteria for SLE) with resultant ESRD on hemodialysis. No serology tests were found in the available medical records. She was subsequently found to have a positive HIV test although she denied risk factors for HIV [e.g., intravenous drug abuse (IDU)]. Her CD4+ lymphocyte count was 700 cells/μl after the HAART in 2004 when both her AIDS and SLE were clinically stable.

Case no. 4: RA
A 45-year-old man was found to have HIV (presumed to be heterosexually transmitted) 1 year prior to the diagnosis of RA. He had a history of RA that fulfilled ACR 1987 classification criteria in the medical records in 1997 (8 years prior to this presentation) when a rheumatologist recorded the patient had arthralgia, swelling, and tenderness involving the right elbow, wrist, and metacarpophalangeal (MCP) joints with left MCPs, wrist and elbow being deformed. During hospitalization in 1999, he was noted to have bilateral knee synovitis and hand changes including ulnar deviations, swan-neck, and boutonniere deformities while on HAART. There was an erythrocyte sedimentation rate (ESR) of 50mm/h and a negative rheumatoid factor. Radiographs of the right wrist and elbow were reported to have joint space narrowing, periarticular osteoporosis and osteopenia but no erosions. An arthrocentesis of the knee was non-diagnostic. He was treated on prednisone 20 mg daily for RA.

Case no. 5: PM
A sexually active 61-year-old man with a history of IUD was found to have HIV in 1990. On presentation, the patient had a 6-month history of myalgia and proximal muscle weakness of both upper and lower extremities. He had been receiving HARRT for 4 years. Laboratory tests revealed an ESR of 95 mm/h, serum creatine kinase (CK) 930 (normal 24-182) U/L and aldolase 26 (normal 1.9-7.3) U/L. Electromyography (EMG) showed moderate to severe denervation (fibrillation and positive waves) with small, short, and polyphasic motor unit potentials, consistent with inflammatory myopathy. Muscle biopsy demonstrated multiple scattered patchy areas of chronic inflammatory cell infiltration with focal necrosis. This case satisfied Bohan and Peter Criteria. There was no improvement in muscle weakness with discontinuation of Zidovudine (AZT). The patient subsequently improved on oral prednisone 50 mg daily.

Case no. 6: SSc
A 45-year-old woman had a diagnosis of SSc for 5 years based on the presence of fingertip and toe pain, progressive stiffening of the skin of the face and the extremities, and mask-like face. The patient also complained of dysphagia and dyspnea. She had chronic renal insufficiency of unspecified etiology. Work-up included a normal chest radiograph. Five years after the diagnosis of SSc, she was found to have HIV/AIDS transmitted by a heterosexual partner. There seemed to be no apparent changes in SSc in association with the development of AIDS although she was on the HARRT. The patient was lost to follow-up.

AVN
A total of 6 of 888 (0.7%) cases of HIV/AIDS had AVN confirmed with MRI imaging (Table III). All were found to have AVN after HIV/AIDS was diagnosed and HARRT initiated. There was no history of alcoholism, high dose corticosteroids, CTDs or trauma although prednisone (20 to 30 mg/day) of unclear duration was documented in 3 cases. One case initially had core decompression surgery and then left hip arthroplasty. One case had left total knee replacement due to medial femoral condylar collapse. The remaining cases were treated with analgesics.
Table III. Osteonecrosis in the HIV infected patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age years</th>
<th>Race</th>
<th>Location</th>
<th>Onset year</th>
<th>Duration year</th>
<th>HIV Dx year</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>47</td>
<td>B</td>
<td>Hips</td>
<td>2000</td>
<td>6 Yr</td>
<td>1998</td>
<td>HAART+G</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>44</td>
<td>W</td>
<td>Hips</td>
<td>2004</td>
<td>2 Yr</td>
<td>1987</td>
<td>HAART+G</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>41</td>
<td>B</td>
<td>Lt knee</td>
<td>2001</td>
<td>5 Yr</td>
<td>1992</td>
<td>HAART</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>53</td>
<td>T</td>
<td>Rt hip</td>
<td>2005</td>
<td>2 Wk</td>
<td>2001</td>
<td>HAART</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>40</td>
<td>B</td>
<td>Knees</td>
<td>1998</td>
<td>4 M</td>
<td>1995</td>
<td>HAART</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>56</td>
<td>B</td>
<td>Shoulder</td>
<td>2004</td>
<td>7 M</td>
<td>1994</td>
<td>HAART+G</td>
</tr>
</tbody>
</table>

B: Black; W: White; T: Turkish; HIVDx: HIV diagnosis; Wk: week; M: months; Lt: left; Rt: right; G: glucocorticoid.

**Arthralgia/arthritis and skeletal infections**

In the 888 inpatients, there were 49 (5.5%) of cases of poorly defined arthralgia/arthritis without specific rheumatic diseases and 9 cases (1.0%) of septic arthritis including 7 knees, 1 shoulder, and 1 ankle. Eight cases (0.9%) of osteomyelitis were recorded. No case of spondyloarthritis was identified.

**Discussion**

In this retrospective chart review of 888 HIV/AIDS inpatients, we found 80 (9%) with a variety of rheumatic diseases. The distribution of ethnic groups in our study was similar to a prior report in the general American HIV population (9).

**Coexistence of HIV and SLE**

SLE with HIV appears uncommon. The first case was reported by Kopelman et al in 1988 (10). We have been able to find 32 case reports including 2 patients with discoid lupus erythematosus (11). It was reported that active SLE and HIV/AIDS might be mutually exclusive (11); this was based upon the reported lower incidence of these two concurrent disorders than SLE alone. We found 3 women with SLE and HIV/AIDS, higher than might be expected, as the prevalence of SLE in the general population has been reported to be 40-122/100,000 in the United States (12) and 70/100,000 in China (13). It has been recently reported that 10 cases of lupus-like syndrome with renal involvement in half were found in 98 cases of HIV (14). In additional support of a higher than previously reported concurrent disease is a case report of reactivation of SLE after initiation of the HARRT for AIDS (15).

It should also be noted that SLE shares clinical and serologic findings with HIV (21). For instance, proteinuria and renal failure may occur in both HIV and SLE. HIV associated nephropathy is characterized by a constellation of pathologic findings including a collapsing glomerulopathy, tubular dilatation, and interstitial infiltrate with leukocytes. In the pathogenesis of HIV associated nephropathy, the viral protein nef may play a critical role (22). Our 3 SLE cases developed renal failure with class III lupus nephritis in case no. 1. Renal biopsy is important in differentiating SLE- from HIV-associated nephropathy in some difficult cases. Unfortunately, no renal biopsies were performed in 2 of our cases.

To date, there are no therapeutic guidelines for SLE in the face of HIV infection. Hydroxychloroquine (HCQ) (23) and cyclosporine (24) have been reported to inhibit HIV infectivity in vitro whereas cyclophosphamide treatment for SLE nephritis may lead to the rapid increase of HIV plasma viral load. The fact that more SLE flares were documented during early infection of HIV (e.g., case no. 1) in our present work suggests that SLE may have more disease activity in the early and less advanced infection with HIV infection. Overall, active SLE may be treated with HCQ, corticosteroids, or cyclosporine alone or in combination. Cyclophosphamide (25) should probably be avoided unless necessary. In later stages of HIV infection, treatment of SLE may not need to be aggressive.

**Coexistence of HIV and RA**

Since 1988, RA has been reported to be coexistent with HIV infection, although the concomitant disease appears lower than those of coexisting SLE and HIV. Early reports (26, 27) suggested that RA could remit in the face of HIV infection. More recent reports (28-30), indicate that active RA may coexist with HIV infection. Our patient with RA remained clinically active, and even became disabled after several years of the diagnosis of HIV/AIDS. One explanation for such a discrepancy in the severity of RA between the early and recent reports would be an initial decrease of CD4+ T cells following HIV infection.
and subsequent increase of pathogenic CD4+ T cells with HAART. This is in line with the view that RA is a CD4+ T lymphocyte mediated disease (31). A reduced disease activity of RA with HIV/AIDS on HAART may be due to protease inhibitors since they have been reported to inhibit Toll-like receptors 2 and 4, implicated in the pathogenesis of RA (32). There is little agreement in the therapy of RA with HIV/AIDS; however, Indomethacin, HCQ, and sulfasalazine may be beneficial and safe (33). Interestingly, a TNF alpha inhibitor, etanercept, has been recently reported to be successful in treating a RA patient unresponsive to conventional disease-modifying antirheumatic drugs, who developed AIDS with viral load controlled by HAART (34).

**Coexistence of HIV and PM**

HIV-associated myopathy includes PM, dermatomyositis, AZT myopathy, necrotizing noninflammatory myopathy, rhabdomyolysis, and pyomyositis (35-37). The myopathies can occur at any stage of HIV infection. HIV associated PM has been estimated to be less than 1% and its clinical and pathological findings are indistinguishable from autoimmune PM in a non-HIV population (38). In a longitudinal study of 64 HIV patients with muscle weakness and/or elevated CK by Johnson RW et al. (37), it has been reported that 13 cases (20%) had biopsy proven myositis and eight of the 13 patients had necrotizing myopathy with polyphasic small motor unit potentials, fibrillations, and increased insertional irritability by EMG. By muscle biopsy, all the 13 patients had mononuclear infiltrates with fiber atrophy in 7 and necrosis in 4. While predominantly CD8 T lymphocyte infiltrates in muscle specimen are seen in both HIV-positive and non HIV PM, a significant decrease in endomysial CD4+ T lymphocytes is more prominent in HIV associated PM (39). We found only 1 case of PM that occurred 10 years after the diagnosis of HIV. Currently the treatment of HIV-associated PM is similar to that of PM in non-HIV population although HIV associated PM has been reported to respond well to corticosteroids and immunosuppressive therapy including azathioprine/methotrexate and intravenous immunoglobulin, and it may carry a relatively favorable prognosis. AZT can induce myopathy and it is clinically indistinguishable from PM; however, AZT has been shown to cause ragged red muscle fibers due to its mitochondrial toxicity (40). AZT withdrawal is an effective therapeutic option. The myositis in our case did not respond to the cessation of AZT.

**Coexistence of HIV and SSc**

We have been able to find 1 prior report of SSc and HIV/AIDS (41). In this case, the ANA was 1:320 and the anti-Scl 70 antibody was negative. It was not clear if HIV predated Ssc. A decrease in skin tightening and frequency of Raynaud’s attacks with CD4+ lymphocyte increase was observed after 6 months of the HAART. Our case was a woman with a 4-year history of SSc before HIV was detected. The clinical features such as skin changes, dysphagia as well as renal insufficiency did not change with the progression of HIV/AIDS and HAART. The pathogenesis of concurrent SSc and HIV is unknown; however, retroviral conserved pol sequences have been identified in the sera of patients with SSc, suggesting that HIV pol sequences may correlate with the development of autoimmune response to U1-70 kDa polypeptide antigen (42).

**Coexistence of HIV and AVN**

AVN has been reported with higher frequency (0.3-0.45%) in HIV patients than the general population (43-45). In a French study involving 56,393 HIV subjects with a total follow-up of 229,031 person-years, symptomatic AVN was diagnosed in 104 subjects with an incidence of 4.5/10,000 person-years (46). In another report (44), an MRI screening study for hip AVN was performed in 339 asymptomatic HIV-infected adults and 118 age-and sex-matched controls, AVN was present in 4.4% of asymptomatic HIV-infected with none in controls. To date, there have been several case reports on AVN in HIV infected patients (47, 48). For example, Reddy et al. have reported 3 cases of AVN in 160 patients with HIV (47). We have found 6 cases of symptomatic AVN in 888 inpatients with a prevalence of 0.7%. Overall, risk factors associated with AVN include HIV infection (46), HAART (46) and a history of glucocorticoid/anabolic steroid exposure (44). All 6 cases in our case were all on HAART with 3 having been exposed to glucocorticoid therapy. Taken together, these data indicate that AVN has become a potential treatment related complication in the scenario of HIV/AIDS and its occurrence may be associated with the HIV itself, HAART (protease inhibitor), corticosteroids, (49, 50), and/ or anticardiolipin antibody (44).

**Coexistence of HIV and spondyloarthritis**

Seronegative spondyloarthritis subsets such as ankylosing spondyloarthritis, reactive arthritis, and psoriatic arthritis were relatively common in an HIV infected African population (51-53). For example, in Zambia, the prevalence of spondyloarthritis was calculated to be approximately 180 in 100,000 in HIV positive people and 15 in 100,000 in HIV negative population. Reactive arthritis (4-10%) and psoriatic arthritis (2-6%)
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were 4%-10% and 2%-6% respectively (54). In North America, spondyloarthritis in association with HIV infection were uncommonly reported (55). There were no spondyloarthritides subsets found in our study although 2 cases of psoriasis were documented before 1995. Taken together, these data suggest that the prevalence of spondyloarthritides in HIV infected patients may be rare in North America, especially in HAART era (8). TNF alpha inhibitors, etanercept and infliximab, have been recently reported to be effective in 3 cases of psoriatic arthritis with AIDS while viral loads were well controlled by HAART and well tolerated (56, 57).

Arthralgia/arthritis and skeletal infections

In addition to nonspecific arthralgia, arthritis associated with HIV/AIDS includes HIV associated arthropathy. This is described as: 1) primarily oligoarthritis of the lower extremities, 2) painful non-specific articular symptoms with sharp and excruciating pain in the knees, shoulders, and elbows lasting approximately less than 24 hours (58), and 3) Jaccoud arthropathy (59). Our prevalence of 5.5% arthritis/arthralgia is in the range of reports prior to 1995 (0.4% to 12%) (4, 6, 60-62). The etiology of these arthritic symptoms and findings are unclear. They have been known to be non-inflammatory and seem to respond to reassurance and non-narcotic analgesics. Most are self limited, lasting less than 6 weeks (63).

In the present study, septic arthritis and osteomyelitis accounted for 1% and 0.9% of the 888 cases of HIV. In a prospective study of 75 patients with HIV infection referred to a rheumatology clinic in New Orleans, Marquez et al. reported septic arthritis in 6 cases (8%) and osteomyelitis in 15 (20%) (64). The discrepancy in skeletal infection rate between the 2 studies could be high referral bias and other high risk factors in their report. The skeletal infections are mostly caused by <i>staphylococcus aureus</i> related to IUD (65).

**SS and diffuse infiltrative lymphocytosis syndrome (DILS)**

SS is a systemic autoimmune disease affecting the exocrine glands such as the parotid glands, and its occurrence in HIV/AIDS was first reported in 1985 (66). DILS appears to be a variant characterized by CD8 T lymphocytosis in blood, tissues, and internal organs, initially reported in HIV infection by Itescu in 1989 (66). It has been reported that the prevalence of SS in the general population is 0.33-0.77% (67). The prevalence of SS and DILS in HIV population is 7.79% and 3%-4% respectively, and their rates in HIV may be decreasing as reported in the recent literature (68). There were no cases of SS and DILS found in our study. While SS and DILS share some clinical and laboratory findings, there are features that may aid in differentiating between the two diseases (69). It should be pointed out that both SS and HIV have been reported to have a high rate of lymphoma, NHL in particular, but most of the cases of the NHL in association with SS are low grade marginal zone lymphomas of the salivary glands and other extranodal sites (70).

**HIV-associated vasculitis**

Vasculitis has been uncommonly associated with HIV infection (71). Several types of vasculitis reported in the literature (72,73) include polyarteritis nodosa, leukocytoclastic vasculitis, microscopic polyangiitis, granulomatous necrotizing vasculitis of central nervous system, Kawasaki-like syndrome, cryoglobulinemia, eosinophilic vasculitis, and lymphomatoid granulomatosis. For example, Zhang et al. (14) have reported 20 cases of vasculitis (20.41%) in 98 inpatients with HIV/AIDS, including 15 Behçet-like disease, 2 Henoch-Schönlein purpura, 2 digital gangrene, and 1 central nervous vasculitis. In another report (72), 11 cases of palpable purpura have been found in 62 cases of HIV patients.

**Hypotheses of potential mechanisms with regards to HIV infection and autoimmune rheumatic diseases**

The mechanisms linking HIV with certain rheumatic diseases is unclear. A possible explanation involves direct viral invasion of endothelium (74), synovium, and hematopoetic cells, resulting in expression of new autoantigen(s) (75). Another hypothesis involves molecular mimicry where infectious agents, such as HIV, has molecular similarity to a human self antigen, inducing autoimmune responses (75). The latter theory is supported by sera of SLE and SS patients that contain antibodies to HIV p24 protein in the absence of HIV infection (76). Additional support for mimicry is that in HIV, polyclonal B cell activation and expansion generate several autoantibodies including ANA and anticardiolipin (44,72). There are also elevated circulating immune complexes (72). In advanced stage of AIDS, immune reconstitution after anti-retroviral therapy results in autoimmune activation; this is characterized by high levels of proinflammatory cytokines and activated CD4+ and CD8+ T cells that appear to lead to autoimmune diseases such as vasculitis (73).

**Limitations of our study**

The study is a retrospective chart review. Although the ICD discharge diagnostic codes were considered to be quite complete, not all patient information may have been adequately recorded in the medical records. Rheumatology consultation was not performed on all patients and it is possible some rheumatic manifestations were not fully reported. Therefore, certain rheumatic diseases in association with HIV/AIDS such as SS, DILS, etc. may be underdiagnosed. There was no comparison or control group and all information was from a single center, perhaps implicating selection bias.

In conclusion, our data of this largest sample size of HIV/AIDS support the previous reports that various rheumatic diseases may coexist with HIV infection. There have been emerging new complications such as AVN and there may appear to be a tendency of more CTDs and less spondyloarthritis in the HIV population. In conjunction with the literature, it would be reasonable to state that the clinical patterns of rheumatic manifestations in HIV infected patients may have been changed since the introduction of the HAART. This would enrich our knowledge of diagnosing and managing the rheumatic conditions in HIV infection.
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