

# Orthopedic Illnesses in Patients with HIV

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## KEYWORDS

• HIV infection • Musculoskeletal disorder • Orthopedic illnesses

HIV infection and the medications used to treat it can cause a wide range of musculoskeletal problems.<sup>1</sup> Patients infected with HIV are susceptible to most of the same types of fractures, dislocations, and other musculoskeletal disorders as patients without HIV. However, there are several musculoskeletal conditions that are specific or unique to the patient infected with HIV.

The advent of antiretroviral therapy (ART) has changed the course of the disease. AIDS was transformed from an invariably fatal condition to a chronic manageable disease in developed countries.<sup>2,3</sup> This disease shift was accompanied by a corresponding change in the types of musculoskeletal complications that patients infected with HIV may experience. For example, there has been a decrease in opportunistic infections of the bone, and an increase in osteopenia and osteonecrosis.<sup>4,5</sup>

HIV, the immune response, and medications can be directly toxic to the bones, joints, and muscles. The cellular immune system is compromised and unusual organisms and malignancies can affect the host. Infections tend to present at a more advanced stage because of the underlying immune status of the patients. Certain rheumatologic conditions such as reactive arthritis (formerly Reiter syndrome) also seem to be more common in this patient population. The specific musculoskeletal conditions affecting the patient infected with HIV may be divided into 4 categories: disseminated diseases, bone disorders, joint disease, and myopathies.

## DISSEMINATED DISEASES

### *Neoplastic*

Immunosuppression predisposes patients to malignancy. Kaposi sarcoma (KS) and high-grade non-Hodgkin lymphoma (NHL) are prototypical AIDS-defining malignant diseases. A conservative estimate suggested that AIDS increases the risk of KS by

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at least 310 times and NHL by more than 110-fold.<sup>6</sup> KS is a vascular neoplastic disease that primarily affects the skin, causing cutaneous violaceous nodules or plaques. It can involve a variety of sites including the lymph nodes, lungs, liver, and spleen. Epidemic KS is the most common AIDS-associated cancer in the United States.<sup>6,7</sup> There are rare reports of KS involvement of bone.<sup>8</sup> Generally, osseous KS is usually believed to be the result of contiguous invasion from nearby tissues.<sup>9</sup> KS lesions are not well visualized on plain radiographs. Other modalities such as computed tomography (CT) scan, magnetic resonance imaging (MRI), and nuclear studies are more helpful. The diagnosis should be confirmed with a biopsy of the lesion.

NHL in patients with AIDS tends to be of the aggressive B-cell type that is associated with pronounced immunosuppression. The bone marrow is involved in up 30% of cases.<sup>10</sup> Symptoms are variable and nonspecific. However, lymphoma presentation is often late, and patients present commonly with fever, night sweats, and weight loss. Treatment of neoplastic diseases in HIV patients involves a team approach with an HIV specialist and an oncologist experienced in treating patients with AIDS. Treatment includes ART as well as cytotoxic drugs in NHL and widespread KS.

## **Infectious**

### ***Mycobacteria***

Patients infected with HIV are at much higher risk for primary or reactivation of *Mycobacterium tuberculosis* (TB). The global epidemic of HIV resulted in large increases in tuberculosis (TB) rates and TB is the leading cause of death in persons infected with HIV worldwide.<sup>11</sup> HIV infection is also the highest risk factor for progression from latent TB to active disease.<sup>12</sup> TB primarily affects the pulmonary system, but in patients infected with HIV extrapulmonary manifestations are common, and may be concurrent with pulmonary TB.<sup>11,13,14</sup> Tuberculosis has many musculoskeletal manifestations including spondylitis, septic arthritis, osteomyelitis, and bursitis.<sup>13</sup> Extrapulmonary tuberculosis is believed to be the result of hematogenous dissemination and seeding of remote sites by the mycobacterium. A common site for musculoskeletal tuberculosis is the lower thoracic or the upper lumbar segments of the vertebral column (Pott disease). A case series from Zambia revealed that two-thirds of patients with musculoskeletal TB had spinal involvement (**Table 1**).<sup>15</sup>

Untreated tuberculous spondylitis results in progressive inflammation and necrosis of the bone, causing vertebral collapse. Ten percent of these patients can develop neurologic complications.<sup>1</sup> Large paraspinal abscesses are also characteristic of TB. There can also be soft tissue extension leading to psoas muscle involvement.<sup>1</sup>

<b>Location</b>	<b>n (%)</b>
Spinal disease	124 (66)
Hip disease	35 (18)
Knee	19 (10)
Other joints	9 (6)
Other bone	2 (1)

Data from Jellis JE. Orthopaedic surgery and HIV disease in Africa. *Int Orthop* 1996;20(4):253–6.

MRI of the spine is the initial diagnostic modality of choice, as plain film findings may be absent. A bone biopsy will confirm the diagnosis.

Tuberculosis can also seed a joint space causing septic arthritis. It preferentially affects the large weight-bearing joints such as the hip and knee (see **Table 1**). In these cases the patients often have concurrent osteomyelitis and soft tissue involvement.<sup>13</sup> Clinical findings are nonspecific and a bone biopsy with a positive tuberculin skin test is needed to make the diagnosis.

Atypical mycobacterial infections are a manifestation of advanced AIDS. They are not as pathogenic and the risk of systemic dissemination increases when the CD4 count decreases to less than 100 cells/mm<sup>3</sup>.<sup>16</sup> There are many reports of musculoskeletal infections from atypical mycobacteria in the literature. These infections occur late in the disease process and are often associated with other opportunistic infections. Atypical mycobacterial infections generally spread hematogenously and often involve several joints or bony sites. Even though *Mycobacterium avium complex* is the most common atypical mycobacterial infection in patients with HIV, *Mycobacterium kansasii* and *Mycobacterium haemophilum* have more of a predilection for the musculoskeletal system. Cutaneous lesions such as nodules and ulcers are often present and may be a clue to the diagnosis.<sup>13,17</sup>

### **Bartonella**

Bacillary angiomatosis (BA) is a disseminated infection that is caused by *Bartonella henselae* and *Bartonella quintana*. The organism involved is a rickettsia-like organism. In the immunocompetent host, *Bartonella henselae* cause a local self-limited lymphadenitis. It is associated with cutaneous and visceral involvement in those with advanced AIDS. The vascular proliferative lesions in the skin are difficult to distinguish clinically from KS.<sup>18</sup> Involvement of the lymph nodes, central nervous system (CNS), liver, and osteomyelitis, especially in the long bones<sup>1,13</sup> occur in advanced AIDS. In fact, osteomyelitis may differentiate BA from KS as bony involvement is an unusual manifestation of KS. Again, the diagnosis is made with a bone biopsy, and antibiotic therapy can be curative. Untreated disease can be fatal.

## **BONE DISORDERS**

### ***Osteopenia and Osteoporosis***

Normal bone undergoes continuous remodeling, with matched bony resorption and new bone formation. Multiple studies have suggested patients infected with HIV have lower bone mineral density (BMD) than age-matched controls.<sup>4,19,20</sup> The causes are many, and include the disease itself as well as medications.

BMD can be measured using dual x-ray absorptiometry (DXA), single x-ray absorptiometry (SXA), and quantitative CT scan. Osteoporosis is defined by a bone density that is greater than 2.5 standard deviations (SD) from normal, which is based on a young control group. Osteopenia is defined as a BMD that is 1 to 2.5 SD less than normal. The reduction in the strength of the bone leads to an increased risk of fractures.<sup>20</sup> In 1 recent series, fractures of the spine, hip, and wrist were significantly more common in patients infected with HIV than in controls with no HIV infection (**Table 2**). The pathogenesis of osteoporosis is complicated and multifactorial.

ART, especially protease inhibitors, have been linked to the development of osteopenia and osteoporosis.<sup>4,20</sup> In addition, HIV is now believed to be an independent risk factor for reduced BMD. Currently, bone densitometry is recommended in women infected with HIV aged 65 years or older and in younger women with additional risk factors for premature bone loss.<sup>21</sup> Osteoporosis is often under diagnosed in men and HIV is a significant risk factor.<sup>22</sup>

	Infected with HIV	Not Infected with HIV
Total fractures	2.87/100 persons	1.77/100 persons
Vertebral	1.01/100 persons	0.47/100 persons
Hip	0.72/100 persons	0.51/100 persons
Wrist	1.38/100 persons	0.90/100 persons

Data from Triant VA, Brown TT, Lee H, et al. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV infected patients in a large U.S. healthcare system. *J Clin Endocrinol Metab* 2008;93(9):3499–504.

### **Osteonecrosis**

Osteonecrosis, previously known as avascular necrosis, refers to bone infarction at the epiphyseal regions of a bone near a joint. The incidence of osteonecrosis is up to 45 times greater in patients infected with HIV.<sup>23</sup> Traditional predisposing factors include hypertriglyceridemia, corticosteroid use, and ethanol abuse. ART, especially protease inhibitors, have also been implicated.<sup>1,4,23</sup> Osteonecrosis occurs most often in the femoral head, but may occur in other locations. Although the risk factors have not been completely elucidated, a lower CD4 count and a history of corticosteroid use are associated with its development.

Unfortunately, benign musculoskeletal complaints are common in HIV patients, but the emergency physician must maintain a high index of suspicion in patients presenting with severe, persistent, or unusual pain. Routine radiographic screening in asymptomatic patients is not recommended.<sup>21</sup> MRI of the hip is recommended in patients with persistent pain and in those who have abnormal plain radiographs. Orthopedic referral is needed in those patients with a suspicion of osteonecrosis.<sup>21,23</sup>

### **Osteomyelitis**

Osteomyelitis, or infection of the bone, is a heterogeneous disease process and may result from hematogenous spread of a remote infection, local spread of a contiguous focus of infection, or direct inoculation.<sup>24</sup> The disease may be divided into acute and chronic forms. Excluding BA, osteomyelitis in the patient infected with HIV is similar to that in patients without HIV, and is a relatively uncommon complication. However, when osteomyelitis occurs, many organisms have been reported in the patient infected with HIV, including *Salmonella*, *Cryptococcus*, *Nocardia*, and *Candida albicans*.<sup>25</sup> TB osteomyelitis is extremely common in endemic areas, especially when the lesion involves the vertebral column.<sup>13</sup> In most cases, patients are afebrile and present with back pain.

Conventional radiographs should be the first step in imaging patients with suspected osteomyelitis. When positive, they are helpful; however, normal plain films are unable to exclude the diagnosis of osteomyelitis. A 30% to 50% reduction in bone density must occur and it can take 3 weeks for a lesion to become visible on plain films. MRI and nuclear imaging are much more sensitive and specific. MRI has become the imaging modality of choice in evaluating osteomyelitis, especially that of the vertebral column. Sensitivity is reported to be between 82% and 100% with a specificity of 75% to 96%.<sup>25</sup> The diagnosis is made definitively by a bone biopsy and culture. Blood cultures may be positive in bacterial osteomyelitis in cases resulting from hematogenous spread. Treatment involves long-term antimicrobial therapy and sometimes surgical debridement.<sup>24</sup>

## JOINT DISEASE

### **Septic Arthritis**

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Septic arthritis is relatively uncommon in patients infected with HIV. Risk factors include intravenous drug use or hemophilia.<sup>5,13,26</sup> Infection of the joint can occur by the same mechanisms as osteomyelitis. The most common organism is *Staphylococcus aureus* regardless of HIV status. Tuberculosis is a common cause of septic arthritis in developing countries.<sup>27</sup> Although still rare, the risk for atypical infections, such as *Sporotrichosis schenkii* and *Candida albicans*, increases in advanced HIV.<sup>13</sup> Gram-negative bacilli such as *Pseudomonas aeruginosa* are found in increased incidence in patients who use intravenous drugs.

Disseminated gonococcal infection causes septic arthritis in sexually active adults. Polyarticular disease from gonococcus is more common in patients infected with HIV. The large weight-bearing joints are most often affected. Arthrocentesis and synovial fluid analysis is the mainstay of diagnosis. Patients with CD4 counts that are less than 200 cells/mm<sup>3</sup> may also have a lower joint fluid white blood cell count, making the diagnosis even more challenging.<sup>26</sup> Isolating the organism is difficult especially in atypical infections. Occasionally synovial biopsies are needed as well as special stains. Empiric treatment should be directed at methicillin-resistant *Staphylococcus aureus* (MRSA) as this is emerging as the most common cause of bacterial septic arthritis.<sup>26,28</sup>

### **Spondyloarthritis**

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Patients infected with HIV have a higher incidence of spondyloarthropathy than the general population. These include HLA-B27 associated reactive arthritis and psoriatic arthritis. Reactive arthritis is 100 to 200 times more common in the patient infected with HIV compared with a non-infected host.<sup>29</sup> However, some believe that the association of reactive arthritis with HIV is related to sexual activity and generalized immune suppression rather than the virus itself.<sup>30</sup> Reactive arthritis is associated with genitourinary and gastrointestinal infections like *Chlamydia trachomatis*, *Campylobacter jejuni*, and *Shigella flexneri*. Classically reactive arthritis presents with the triad of arthritis, urethritis, and conjunctivitis. Patients infected with HIV suffer a more severe and debilitating course of this disease and the classic triad is often absent.<sup>1</sup>

Psoriatic arthritis is up to 40 times more common in the host infected with HIV.<sup>29</sup> Patients may have typical changes in the skin (scaled maculopapules) of the elbows, scalp, trunk, and knees. Psoriatic arthritis is more common in those with advanced HIV disease and the skin findings are more extensive than in patients with no HIV infection.<sup>31</sup> Psoriatic arthritis often involves the surrounding tendons and fascia (enthesopathy). The management of these conditions can be difficult. Nonsteroidal antiinflammatory drugs (NSAIDs) are the first choice but are often not effective. Sulfasalazine has been effective in some cases, and occasionally immunosuppressive agents are indicated, which is problematic in this population. Effective ART is also helpful in treating these inflammatory conditions.<sup>31</sup>

### **HIV-associated Arthritis**

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HIV infection is associated with an arthropathy similar to other viruses (eg, hepatitis B). It is typically a transient, nonerosive, oligoarthritis that affects the lower extremities, lasting less than 6 weeks. It can occur at any time during the course of HIV infection. Synovial fluid analysis is noninflammatory. Rheumatoid factor and antinuclear antibodies tests are negative in this condition. The treatment consists of NSAIDs, and

the condition tends to be self-limited.<sup>31,32</sup> Painful articular syndrome has been described in patients infected with HIV. It is characterized by an acute onset of severe arthralgia, a self-limited condition that usually lasts less than 24 hours. Like HIV-associated arthropathy, the synovial fluid analysis is unremarkable.<sup>31</sup>

## MYOPATHIES

### *Polymyositis*

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Polymyositis can occur at any stage of HIV infection. It is an idiopathic inflammatory process of the skeletal muscle.<sup>31,33</sup> Patients present with a subacute, progressive, proximal muscle weakness with an increased creatine kinase level. It may be the first sign of HIV infection. Treatment with corticosteroids seems to be beneficial as it is in other inflammatory myopathies. Medications such as high-dose zidovudine (AZT or ZDV) are associated with a polymyositis-like picture in a small percentage of patients. Zidovudine-induced myopathy is initially clinically indistinguishable from polymyositis. Clinical and laboratory features normalize several months after discontinuing therapy.<sup>29</sup>

### *Pyomyositis*

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Pyomyositis is a primary deep muscle abscess seen more often in patients infected with HIV than those with no HIV infection. *Staphylococcus aureus* is the culprit organism in more than 90% of cases.<sup>1</sup> The inciting factor of the infection is unclear. It has been postulated that a transient bacteremia seeds traumatized muscle.<sup>13</sup> The disease is indolent, and initially patients complain of crampy pain along 1 muscle group, with a low-grade fever.<sup>34</sup> It may be difficult to distinguish from polymyositis or other forms of inflammatory muscle disease. Induration may be present. The most common sites of involvement include the quadriceps, the gluteal, and iliopsoas muscles. After 1 to 3 weeks, the pain becomes progressively worse and the fever more pronounced.<sup>10,13</sup> If undiagnosed, the patient will likely become septic. CT scan, MRI, and ultrasound are all helpful in making the diagnosis. MRI is probably more sensitive early in the course before the fluid collection becomes prominent. Treatment is by drainage and systemic antimicrobial therapy directed at *S aureus*.

## SUMMARY

Various musculoskeletal manifestations can occur in the individual infected with HIV. The spectrum of disease is a result of a combination of the immunosuppressive effects of the virus, the immune response to the virus, and the medications used to treat the disease. ART has altered the course of the disease and this shift has changed the musculoskeletal manifestations. There are now fewer opportunistic infections and an increase in osteopenia and osteonecrosis.

Patients who are profoundly immunosuppressed are predisposed to disseminated and unusual infections, including disseminated bartonella, tuberculosis, and atypical mycobacterial infections. Noninfectious spondyloarthropathies are also more commonly associated with HIV, as are myopathies. The emergency physician must be aware of these specific manifestations of orthopedic disease in the patient with to increase the likelihood of early diagnosis, treatment, and appropriate referral.

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