Musculoskeletal considerations in HIV disease: A critical review

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Abstract

Introduction
The vast progress in management of HIV disease with antiretroviral therapy (ART) in the past three decades has resulted in increased life expectancy for people living with HIV/AIDS. With this new chronicity of the disease has emerged a constellation of musculoskeletal impairments ranging from arthritis to traumatic fractures requiring orthopedic surgery. This manuscript aims to review and critique recent research (2009-2014) investigating musculoskeletal complications of HIV disease, and to propose future directions for management of such diagnoses.

Methods
The literature reviewed was divided into the following categories, in order of publication date: general musculoskeletal complications arising from the HIV virus itself and/or ART, HIV-related bone infections and bone disease, rheumatic disease in HIV infection, vitamin D deficiency in HIV disease, and orthopedic post-surgical complications/risk factors resulting from HIV disease.

Results
A total of 19 articles met the described inclusion criteria and were included in this critical review. From most recent (2014) to oldest (2009), 4 articles were published in 2014, 7 in 2013, 3 in 2012, 1 in 2011, 2 in 2010 and 2 in 2009.

Discussion
While the pathophysiology of HIV-related musculoskeletal complications is well documented in the literature, it is crucial that attention is also focused on treatment. The complex nature of disability in PLWHA necessitates a multidisciplinary approach to treatment to adequately address the diagnostic and treatment needs of this population.

Conclusion
Given the multitude of musculoskeletal complications that arise from the HIV virus and/or ART, research must be continuously conducted to assess risk, prevention and treatment. This research will need to focus on both non-surgical and surgical approaches to management of musculoskeletal complications in the HIV-infected individual.

Introduction
Over the past three decades, the lifespan of people living with HIV/AIDS (PLWHA) has been greatly extended due to the development of anti-retroviral therapy (ART) in the late 1990s. Most patients who take the recommended ART regimen experience immunological improvement and can experience normal life expectancy.1,2 With this increased life expectancy has emerged a symptom burden for PLWHA of impairments such as musculoskeletal and neurological complications and chronic pain.

There is a diversity of literature on varying aspects of HIV, and research has recently focused how the disease—especially given its increased chronicity—affects the musculoskeletal system. This focus is necessary in order to diagnose and properly treat various orthopedic, rheumatologic and pain symptoms and diagnoses amongst PLWHA. This review aims to review and critique recent research (2009-2014) investigating musculoskeletal complications of HIV disease, and to propose future directions for the management of such diagnoses.

Literature suggests that musculoskeletal conditions will affect 72% of HIV-infected individuals during their lifespan.3 Musculoskeletal and orthopedic complications have emerged as potential results of the disease itself and/or the ART treatment regimen. For example, low bone mineral density (BMD) has been associated independently with HIV disease itself and as a direct effect of ART.4 The increased life expectancy of people living with HIV increases the possibility that these individuals will develop age-related arthritis, as well as other chronic musculoskeletal impairments as complications of HIV virus and/or because of expected age-related symptoms.5 Recent research suggests that the probability of PLWHA developing osteoporosis is three times higher compared to their HIV-negative counterparts.6,7 A growing body of literature over recent years has shown that given this loss of BMD, vitamin D deficiency is highly prevalent among people living with HIV.8 Low vitamin D (hypovitaminosis D) is widely known to have detrimental effects on bone health, in addition to cardiovascular, metabolic, immune and neurocognitive functions.

Given the increased bone fragility and fracture risk due to low BMD, PLWHA often require orthopedic surgery for fragility fractures and/or other low BMD-related events. Because of their immunocompromise, research has examined the question of increased risk for perioperative or postoperative infection in this population.9,10,11,12

Methods
An electronic search was performed of the Medline database using the PubMed search engine using the search terms, “musculoskeletal OR orthopedic HIV infections complications”. Inclusion criteria were any articles specifically discussing musculoskeletal/orthopedic considerations and/or complications of HIV disease published in English and with adult human subjects. Date
limits were set to the past five years, as this review seeks to provide a review of current literature and practice.

**Results**

A total of 19 articles met the described inclusion criteria and were included in this critical review. From most recent (2014) to oldest (2009), 4 articles were published in 2014, 7 in 2013, 3 in 2012, 1 in 2011, 2 in 2010 and 2 in 2009. The following categories were identified in the review of the relevant literature: general musculoskeletal complications arising from the HIV virus itself and/or the ART medication regimen (n=4); HIV-related bone infections and bone disease (n=5); Rheumatic disease in HIV infection (n=4); Vitamin D deficiency in HIV disease (n=2) and orthopedic post-surgical complications/risk factors resulting from HIV disease (n=4). Table 1 describes the summarized findings in each category in order of publication date.

**Discussion**

This article reviewed literature published in the last 5 years regarding musculoskeletal complications of HIV disease. Both HIV infection itself and the pharmacological treatment of the disease can cause a wide range of musculoskeletal impairments such as increased risk of fractures, osteonecrosis and spondyloarthropathy. Both HIV and ART have been established as independent risk factors for osteoporosis. The high prevalence of hypovitaminosis D amongst PLWHA puts this population at risk for fractures and osteoporosis/osteopenia, and people with HIV should be screened carefully for low BMD – especially those with a history of bone disease and "traditional" risk factors such as low dietary intake, female sex, dark skin pigmentation and low sun exposure. The establishment of optimal Vitamin D dosing regimens in this population is needed, as well as the impact of such supplementation in preventing comorbidities.

Bone and joint infections account for approximately 67% of musculoskeletal infections in HIV-infected patients. Rheumatic manifestations can include arthritis, spondyloarthritis, diffuse infiltrative lymphocytosis syndrome (DILS), vasculitides, connective tissue disease, myopathies and musculoskeletal diseases. Most anti-rheumatic therapies appear to be safe and effective in HIV-positive patients when used according to protocol. Give the increased chronicity of the disease, a certain percentage of people with HIV will inevitably require orthopedic surgery. A literature review of orthopedic post-operative infections of HIV-positive patients shows only four in the past five years in the United States. There is a need for robust studies examining the effect of reduced CD4 counts and viral load suppression, and prolonged antibiotic use to determine actual risk of infection in PLWHA compared to their HIV-negative counterparts. Certain orthopedic surgeries can greatly improve quality of life and functional outcomes for HIV-positive individuals. Further research is warranted to evaluate pre- and peri-operative measures that may prevent or decrease infection in this population.

**Conclusion**

While the pathophysiology of HIV-related musculoskeletal complications is well documented in the literature, it is crucial that attention is also focused on treatment. With increased life expectancy for PLWHA it will inevitably come normal age-related issues in this population, which may or may not present differently than those experienced by their HIV-negative counterparts. These impairments may range from mildly bothersome to true disability, and healthcare workers across the spectrum will need to be prepared for the increased demands of caring for aging PLWHA. The complex nature of disability in PLWHA necessitates a multidisciplinary approach to treatment to adequately address the needs of this population, drawing on the expertise of physicians, nurses, physical and occupational therapists, mental health experts and nutritionists.

A few recent studies have examined the physical and functional benefits physical therapy interventions and their potential impact within this population. A 2014 study reported that upon surveying HIV physicians, 70% of the sample reported referring patients to PT and 51.5% of those referrals were for musculoskeletal conditions. Due to the well-documented issues of musculoskeletal issues within the HIV-positive population, access to and effectiveness of rehabilitation should be highlighted as a priority area of research in the HIV and rehabilitation domain. The multitude of musculoskeletal complications that arise from the HIV virus and/or ART, research must be continuously conducted to assess risk, prevention and treatment. This research will need to focus on both non-surgical and surgical approaches to management of musculoskeletal complications in the HIV-infected individual.

**References**

The image contains a text document discussing musculoskeletal considerations in HIV disease. The text references studies and their findings, particularly focusing on the impact of ART on bone metabolism and the risk of osteoporosis and fractures in HIV-positive individuals. The document highlights the need for a strategic approach to screening for musculoskeletal infections and comorbidities among HIV-positive individuals, emphasizing the importance of early diagnosis and treatment.

A table summarizing the study characteristics for the critical review is presented, categorizing the studies based on the complications arising from HIV disease itself and/or ART. The table includes references for the studies and their main conclusions, such as the need for preventive care and support in managing musculoskeletal infections and disorders among HIV-positive individuals.

The document also mentions the advancements in HIV treatment and the need for future research examining the interaction between immunity, virus, ART, and bone metabolism. It underscores the importance of providing essential care to both chronic and noninfectious, chronic comorbid diseases among PLWHA, including bone disease.

Competing interests: None declared. Conflict of interests: None declared. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.
The recent emergence of the field of "osteoimmunology" has provided a conceptual framework to explain how the immune and skeletal systems interact. Given that HIV infection and ART are defined independent risk factors for osteoporosis, this framework is imperative in understanding the mechanisms and treatment options for HIV-related skeletal decline. Inflammation and immune dysregulation play a large role in bone turnover and bone loss, which result in osteoporosis and other bone disorders.

Initiation of ART is associated with a decrease in BMD over the first 2 years at a similar magnitude to the BMD loss sustained during the first 2 years of menopause. The causes of low BMD among HIV-infected individuals appear to be multifactorial and representative of a complex interaction between the virus, traditional osteoporosis risk factors and ART-related side effects. The authors propose that HIV infection should be considered an independent risk factor for bone disease. They recommend screening patients with fragility fractures, HIV-infected post-menopausal women, and all HIV-positive men >50 years of age.

The immune restoration inflammatory syndrome upon initiation of ART causes de novo autoimmune, rheumatic disorders among HIV-positive patients. It is controversial whether this is caused by the HIV virus itself, or if the HIV creates "an environmental milieu" that supports these conditions. The authors call for high-quality controlled epidemiological studies using standardized criteria to further investigate the causation of autoimmune disease in HIV disease.

The increased chronicity of HIV disease has precipitated the increase of chronic health problems seen in this already vulnerable patient population. Recent research suggests that the probability of PLWHA developing osteoporosis is three times higher compared to their HIV-negative counterparts. Rheumatologists must be prepared to treat not only HIV-related bone complications such as avascular necrosis (AVN) and osteoporosis, but also take measures to prevent bone loss in HIV-infected patients.

The combination of HIV disease and rheumatic manifestations is the result of a complex web of immunologic, genetic, and environmental factors. Geriatric care for people living with HIV will become increasingly prevalent due to the increased life expectancy of this population. Additionally, younger patients with HIV will likely require years of therapy to address chronic issues such as bone disease.

Rheumatic manifestations in the HIV-positive population can include arthritis, spondyloarthitis, diffuse infiltrative lymphocytosis syndrome (DILS), vasculitides, connective tissue disease, myopathies and musculoskeletal diseases. Anti-tumor necrotic factor (anti-TNF) agents do not appear to adversely affect CD4 count or viral load if the HIV infection is otherwise controlled with ART. Most anti-rheumatic therapies appear to be safe and effective in HIV-positive patients when used according to protocol.

Long-term survivors of HIV disease have an increased risk of developing co-morbidities such as osteoporosis, cardiovascular disease and overall immune dysfunction – all of which are affected by vitamin D levels. Vitamin D supplementation has widely been recommended for PLWHA, however there is a need for future study examining the effect of vitamin D supplementation and CD4 count, insulin resistance/diabetes, and cardiovascular disease.

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<th>Table 1: (continued)</th>
<th>Ofotokun I, McIntosh E &amp; Weitzman MN (2012)</th>
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In addition to “classic” risk factors such as low dietary intake, female sex, dark skin pigmentation and low sun exposure, vitamin D status has been shown to also be associated with HIV-related factors of immune activation and side effects of ART. The authors corroborate the latest EACS guidelines to screen for hypovitaminosis D in HIV-positive individuals who also have history of bone disease, kidney disease or other known risk factors. Vitamin D supplementation/repletion is recommended when 25-hydroxyvitamin D levels fall below 10 ng/ml. The authors call for the establishment of optimal Vitamin D dosing regimens in this population as well as the impact of such supplementation in preventing comorbidities.

The authors examine outcomes of cementless, primary total hip arthroplasty (THA) due to osteonecrosis in HIV-positive patients (n=34) compared with their HIV-negative counterparts (n=70). Results revealed no significant difference in aseptic implant survivorship (at both five and ten-year follow-ups) between the two cohorts. Postoperative Harris hip scores, activity scores, and SF-36 physical and mental component scores were statistically similar between both cohorts. There were two late infections in HIV cohorts and none in the comparison cohort, pointing to this as a potential complication to monitor.

This review examined comorbidities and perioperative complications in HIV-positive patients after primary total hip and knee arthroplasty from 2000-2008, compared with their HIV-negative patients who underwent the same surgeries. The Nationwide Inpatient Sample database estimated that 5,681,024 patients were admitted to hospitals for total hip or knee arthroplasties during this period, 8229 of whom were HIV-positive. There was no statistical difference in total complications for hip or knee replacement surgeries and HIV was not shown to be an independent risk factor for total postoperative infection rate.

Thirty-one HIV-positive, non-hemophiliac patients who underwent total hip arthroplasties (THA) at one hospital during a 12-year period were screened for postoperative complications of deep infection and revision. Results showed that low rates of complications and need for revisions can be achieved in this population and the authors suggest that THA may improve quality of life in some HIV-positive patients who are appropriate surgical candidates.

The authors examined whether there is a higher postoperative infection rate after orthopedic trauma for people who are HIV positive and aimed to identify potential preoperative variables that could predict postoperative infection in people living with HIV. Sixty-four HIV positive patients were assessed who underwent orthopedic surgery requiring instrumentation or implant over a 6-year period in one hospital. Results showed an infection rate of 23% among the HIV positive patients compared with a 3.9% rate for the historical control, HIV negative group. The authors concluded that HIV positive patients with CD4 counts <300 undergoing emergent orthopedic trauma surgery are at greater risk for infection. Other factors associated with postoperative infection were hospital stay, polytrauma and low serum albumin.


