

Approach to Joint Pain in HIV Patients

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Abstract

Background: HIV is associated with high morbidity and mortality, in 2019 there were 38 million people across the globe living with HIV, of which 36.2 million were adults and 1.8 million, children. Generally speaking, HIV infection is associated with a wide variety of clinical presentations, even more when HIV is uncontrolled, or it has reached an advanced stage. Many of the overlapping comorbidities associated with HIV are musculoskeletal with a range of manifestations including reactive arthritis, painful articular syndrome, HIV-associated arthritis being the most frequently encountered.

Findings: Although the pathophysiologic mechanism of HIV arthritides are not fully understood, it is postulated that the HIV virus plays an important role as viral particles have been demonstrated by electron microscopy and by in situ hybridization. In general, viruses can produce arthritis by infecting synovial tissue during systemic infection or by provoking immunologic reaction that involves joint changes and destruction. Directly or indirectly, the HIV virus causes synovial inflammation which leads to joint damage affecting the quality of life among HIV population. HIV arthritides can occur at any phase in the disease course. Inflammatory and reactive arthropathies are more prevalent among HIV positive individuals than in the general population.

Conclusion: HIV arthritides include reactive arthritis, HIV-associated arthritis and painful articular syndrome. Although the pathophysiology is not fully understood, a number of proposed mechanisms have been hypothesized. HIV arthritides differ on their clinical onset, duration of symptoms, number of joints involved, associated symptoms, and management approaches.

Introduction

As of 2019, 38 million people around the world are living with HIV and among these individuals many of them have comorbidities associated with HIV [1]. Many studies have attempted to estimate the incidence and prevalence of musculoskeletal manifestations among HIV patients [2,3]. The knowledge of rheumatic manifestations in HIV has expanded since 1985 when the National Institute of Arthritis and musculoskeletal and skin disease began to investigate the rheumatic complications of HIV disease [3]. The direct role of HIV infection in producing rheumatic manifestations was demonstrated in a longitudinal follow-up of HIV patients; the HIV cohort consisted of 117 patients who were followed for a mean period of 24.6 months [4]. HIV infected patients have a higher risk of developing rheumatic complications, and this can be seen at any stage in the disease [5]. Berman et al. studied 101 consecutive patients living with HIV and discovered 71% had bone, joint or muscle involvement [6].

Musculoskeletal involvement can be seen at any stage of the disease but more likely to manifest in later stages [2]. In the acute phase of HIV infection most patients experience fatigue, fever, maculopapular rash and (50-70%) complain of musculoskeletal manifestations including myalgias, arthralgias and paresthesias, that may be the only symptoms during the acute infection phase [7]. This is why in patients with vague, atypical musculoskeletal complaints, HIV infection should be suspected. Although there is controversy regarding the pathogenetic mechanisms of musculoskeletal disease in HIV, it is evident that HIV associated inflammatory arthropathies worsen as HIV disease progresses.

HIV patients with rheumatic manifestations have reduced quality of life and increased morbidity [2]. A variety of rheumatic syndromes have been reported in association with HIV infection including arthralgia, painful articular syndrome, reactive arthritis, HIV-associated arthritis, psoriatic arthritis, septic arthritis, undifferentiated spondylarthropathy and avascular necrosis of the bone [8].

Publication History:

Received: June 05, 2021

Accepted: June 28, 2021

Published: June 30, 2021

Keywords:

HIV-related reactive arthritis,
Painful articular syndrome, HIV-associated arthritis

HIV-related Reactive Arthritis

The occurrence of reactive arthritis (previously known as Reiter's syndrome) among HIV-infected patients was first published in 1987 [2]; this was followed by reports on a wide scope of rheumatic manifestations and the distinction between the different HIV-associated arthritides. Reactive arthritis has been reported in up to 11% of HIV infected patients, though its prevalence has been shown to vary between different populations [9]. Exposure to bacterial triggers has been postulated to play an important role in the pathophysiology of reactive arthritis (ReA) in HIV. The underlying acquired immunodeficiency allows that microorganisms with arthrogenic potential infect the individuals, enabling the development of ReA [10].

Biomechanical factors might also be involved in disease localization. The enthesis and adjoining structures are subjected to increased biomechanical forces and microfractures which undergo a continuous healing process that is proinflammatory. Enhanced vascularity may favor the deposition of bacteria or their constituent molecules [11]. Factors that help explain these differences are HLA-B27 allele, and the mode of contraction HIV. HLA-B27 have been found to be positive in 80-90% of Caucasians with HIV-associated ReA, while Africans with HIV-associated ReA have been found nearly all to be HLA-B27 negative [12]. Spondyloarthropathies linked to HLA-B27 were

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Citation: Tello D, Pillai M, Gooding K, McFarlane IM (2021) Approach to Joint Pain in HIV Patients. Int J Clin Res Trials 6: 160. doi: <https://doi.org/10.15344/2456-8007/2021/160>

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previously uncommon in Sub-Saharan African populations due to the rarity of HLA-B27, but has since shown an increase in prevalence and severity since the onset of the HIV pandemic associating ReA with HIV rather than HLA-B27. In contrast, in the Caucasian population, since the HIV pandemic, only the severity of ReA has increased rather than the prevalence [13].

The mode of contraction of HIV has also been shown to affect the prevalence of HIV-associated ReA. As with non-HIV infected patients, a history of genitourinary and enteric infections are common and have shown to have higher rates of HIV-associated ReA in populations that acquired HIV through sexual contact compared to populations that acquire HIV through IV drug use [12].

The most typical clinical presentation is asymmetric peripheral oligoarthritis involving the lower extremities accompanied by extra-articular symptoms in 10-50% of the cases [9]. Extra-articular manifestations include mucocutaneous symptoms, ocular inflammation, urethritis, nephritis, and carditis [1,2]. In the majority of patients, the arthritis tends to last 4-5 months but in two thirds of patients (especially those with mild symptoms) the arthritis can span more than a year. In 15-30% of affected patients, chronic arthritis or sacroiliitis can be seen [14]. Similarly, to HIV negative patients with ReA, HIV-associated ReA tends to affect peripheral lower limb joints and enthesitis, but there is an increased probability of extra articular involvement and severe mucocutaneous manifestations such as circinate balanitis, keratoderma, and urethritis. Blenorrhagic dermal keratosis is the most common cutaneous manifestation HIV-related ReA and is characterized by papulosquamous, painless lesions found on plantar and/or palmar regions [15]. HIV-associated ReA is a more serious condition than in HIV negative ReA, showing rapid progression and being more refractory to treatment [8]. Uveitis occurred with around twice the frequency recorded among general population reflecting the accelerated pace at which ReA progresses in HIV infected patients [16].

HIV-associated ReA refers to asymmetric oligoarthritis of lower limbs accompanied by extra-articular mucocutaneous lesions in HIV positive individuals. Abnormal laboratory results frequently found in HIV-associated ReA include leukocytosis, thrombocytosis, anemia, and elevations in hepatic enzymes [17]. Therapeutic management involves NSAIDs and sulfasalazine, while TNF- α inhibitors should be used with caution [18]. Sulfasalazine (1-2 g/day) has been shown to be successful in treatment of HIV-associated ReA without deterioration in HIV infection [19,20]. Bromocriptine has also been reported to decrease inflammation in HIV-related ReA patients who failed to respond to sulfasalazine, although the exact mechanism of action was not well understood [21]. The addition of highly active antiretroviral therapy (HAART) has been shown to lower the severity but not the frequency of HIV-associated ReA. Some authors have suggested that HIV could be prominent in the joint tissues and with HAART successful recovery may be related to inhibition of the virus itself at these sites [22,23]. Another proposed mechanism in HAART is that patients can regain sufficient immune recovery to control pathogens triggering genitourinary or intestinal infections acting as drivers for the disease [22].

HIV-associated Arthritis

HIV-associated arthritis was first described by Rynes et al. in 1988 [23]. These findings were then confirmed by Berman et al. in 1999, when he observed 270 HIV patients and diagnosed HIV-associated

arthritis in 7.8% of them [24]. Direct involvement of the synovial tissues by HIV virus leading to inflammatory infiltrates composed of mononuclear cells and plasma cells. Tubuloreticular structures within the endothelial cells, crystal-like inclusions in plasma cells and virus-like particles are seen in synovial fragments, leading to moderate thickening of vessel walls due to fibromuscular proliferation of the intima which in turn produces ischemia and synovial damage [25]. HIV p24 antigen was detected in the cells of the synovial lining layer however viral culture or identification of viral particles by electron microscopy has not been achieved [26-28]. In one study, HIV DNA had been detected by in situ hybridization techniques within dendritic cells that were isolated from the synovium as well as the peripheral blood of HIV patients [29]. The white cell count in the synovial fluid can range from 50-2600 cells/ μ L and the glucose level tends to be normal [27]. HIV-associated arthritis is characterized as subacute, exquisite tenderness and pain in a varying pattern oligo, mono, or poly-arthritis affecting predominantly the lower extremities (predominantly knees and ankles) that evolves throughout a period of 1-4 weeks [30,31]. Forty-seven percent of the patients had oligoarticular involvement, monoarticular was seen in 38%, and polyarticular in 14% of patients. The condition is self-limited with a mean duration of two weeks, resolving in most patients without sequelae [9]. Studies of the synovium have demonstrated evidence of inflammatory changes, but also non-inflammatory synovium has been reported. Some patients display seronegative arthropathy characteristics with rheumatoid factor, anti-nuclear antibody, and HLA-B27 being negative [9]. Clinical studies reported that none of the affected patients had features of a well-defined rheumatic disease therefore, the term HIV-associated arthritis was found most appropriate. Because of the varied nature of pathologic changes observed in the joints, the treatment also varies and tends to be patient specific. In most cases, arthritis tends to get better by treating the underlying HIV, but symptoms can respond better to analgesics for some while non-steroidal anti-inflammatory medications (NSAIDs) and/or intra-articular corticosteroids provided significant relief [9]. In summary HIV-associated arthritis can have different pathologic, histologic and clinical presentations. Histologically it can range from inflammatory infiltrates of mononuclear cells and plasma cells leading to thickening of vessel walls leading to ischemia and joint destruction with the presence of p24 antigen and HIV DNA detected in the joint in contrast with the non-inflammatory joint histology in select patients. The presentation is highly variable with the number of joints involved ranging from asymmetric oligo- mono, or polyarticular joint involvement that develops over a subacute period of time and is usually self-limiting. Most patients have seronegative arthropathy and usually resolves with analgesics, NSAID, but intra-articular steroid injections have proven to be effective, safe, and be a rapid form of treatment [3].

Painful Articular Syndrome

Painful articular syndrome was first described by Berman et al. in 1988 [6]. Patients with late-stage HIV present with asymmetric, severe, debilitating bone and joint pain that lasts 24 hours but may continue for up to 48 hours. Despite the excruciating pain, signs of inflammation are absent [32,33]. The knee joint is the most commonly affected but shoulder and elbow involvement has also been observed. The pathophysiology underlying painful articular syndrome remains unclear but proposed mechanisms include cytokine production and localized necrosis due to ischemia in the joint [33]. Imaging findings in painful articular syndrome range from no abnormalities to joint effusions that may include periarticular

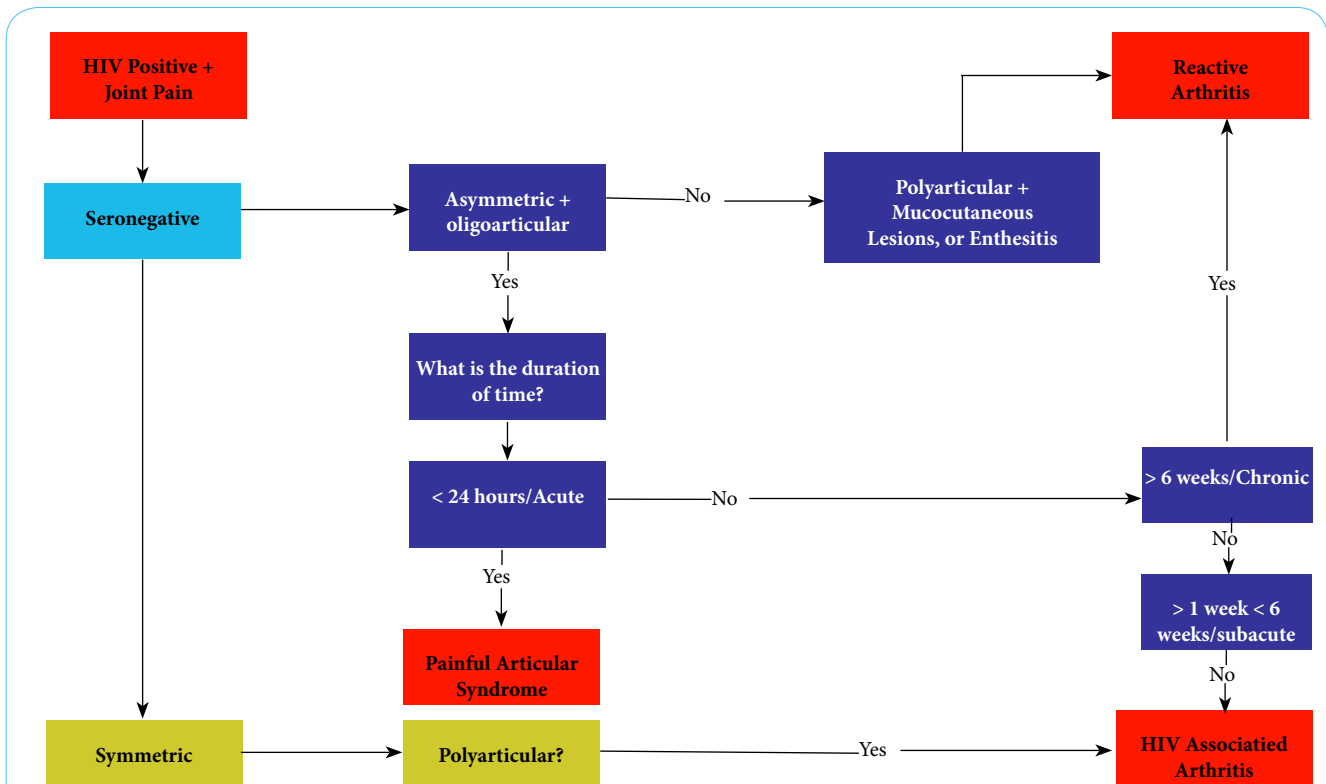


Figure 1: Diagnostic algorithm for HIV Arthritides.

HIV (+) patients should be screened for seropositivity then, consider the number of joints involved and duration of symptoms. Asymmetric involvement that usually lasts <24 hours suggest painful articular syndrome while symmetric, polyarticular joint pain with subacute course of 1-6 weeks suggests HIV-associated arthritis.

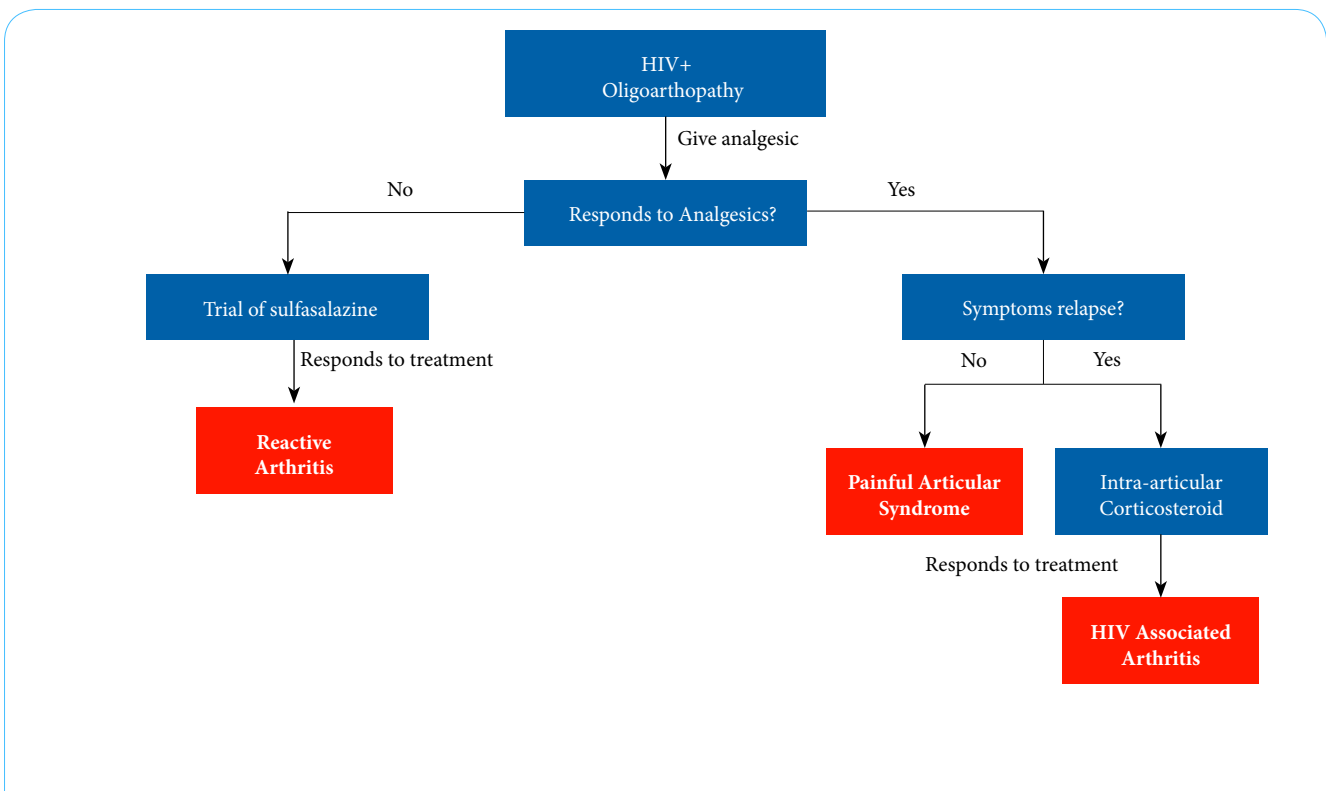


Figure 2: Management algorithm for HIV arthritides.

Reactive arthritis cases tend to respond to sulfasalazine. Painful articular syndrome and HIV-associated arthritis tend to respond to analgesics.

osteopenia but are nonspecific and nondiagnostic [34]. When painful articular syndrome was first reported prevalence ranged from 10% in late-stage HIV patients within the USA and parts of South America with other countries reporting no cases at all [7,35]. Very few case-control studies have been done but a prevalence between 6 and 8% in HIV positive patients compared to HIV negative controls [10]. Other researchers described one case painful articular syndrome among 98 HIV inpatients in China [36] and two patients over a 6-year period had painful articular syndrome at an HIV clinic in Thailand with all patients responding to indomethacin [37]. Cross-sectional studies examining rheumatologic manifestations in HIV positive patients in areas of Africa, including Nigeria and Burkina Faso, did not report any cases of painful articular syndrome [38,39]. Yet, in a cohort study done in India prevalence remains at 3.3% even in patients treated with HAART [40]. Compared to other forms of HIV-associated arthropathies, with the increasing use of HAART, painful articular syndrome has significantly declined in the USA but has still been found to affect up to 2.1% of patients in Southern India [41]. Painful articular syndrome can also be distinguished from septic arthritis due to the intermittent nature of pain presentation, lack of synovitis or joint effusion. If the joint is aspirated, it would reveal a normal percentage of polymorphonucleocytes and lack of inflammatory fluid [3]. Although more than 50% of the patients experiencing painful articular syndrome present to the emergency room due to debilitating pain, symptoms respond to symptomatic analgesic treatment including anti-inflammatories and opioids [42] (Figure 1 and Figure 2).

Conclusion

There are a wide variety of rheumatic syndromes and manifestations associated with HIV disease. This review focuses on some of the articular manifestations seen including Reactive arthritis, HIV-associated arthritis, and painful articular syndrome. Most of these syndromes were first observed in the 1980's and early 90's during the peak of the HIV epidemic [2]. Although the pathophysiologic mechanisms associated with these syndromes are not fully understood, the evidence points to a direct involvement of the virus leading or joint damage as a secondary effect of the inflammation due to the presence of the HIV virus [2]. It is important that clinicians be aware of these syndromes because although the symptoms can be vague they are debilitating and treatment can improve patient's quality of life.

HIV infected patients with vague arthralgias should have a comprehensive history of their HIV disease progression, joint complaints to understand the presentation, localization, associated symptoms, and previous therapies employed. Patients presenting with generalized musculoskeletal complaints should also be tested for HIV at the time of presentation. Treatment with HAART can improve symptoms and impact the morbidity associated with these rheumatic syndromes [9]. Further research is needed on the prevalence of rheumatic diseases associated with HIV, the pathophysiologic mechanisms, and novel therapeutic approaches that can lead to improvement in the care offer to HIV patients.

Competing Interests

The authors declare that they have no competing interests.

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1. UNAIDS.

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