Human immunodeficiency virus infection (HIV)–associated rheumatic manifestations in the pre- and post-HAART eras

Luis E. Vega1 · Luis R. Espinoza2

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Abstract

Rheumatic manifestations remain an important clinical manifestation associated to HIV. To date after 4 decades of the onset of the HIV/AIDS pandemic, almost 37 million individuals are living with the infection, including close to 2 million of newly infected individuals. The status, however, of a considerable proportion of HIV/AIDS patients has changed from a near fatal disorder secondary to opportunistic infections to a chronic disease in which renal cardiovascular, diabetes, malignancy, and autoimmune co-morbid disorders have become prevalent and relevant. In addition, the spectrum of rheumatic disorders also has changed since the introduction of HAART and its diagnosis and treatment represents a challenge. The purpose of this review is to define and discuss the HIV-related rheumatic manifestations in the pre- and post-HAART eras.

Keywords AIDS · Anti-TNF and disease modifying drugs · Arthritis · Bone diseases · Human immunodeficiency virus (HIV) and rheumatic diseases · Immune reconstitution inflammatory syndrome · Rheumatic manifestations · Spondyloarthritis

Introduction

The past few decades have been characterized by the occurrence of several infections, some emerging and other reemerging, despite extraordinary advances in diagnostics, therapeutics, and vaccine development [1, 2]. Several factors contributing to the emergence of recent epidemics have been identified, including genetic adaptations of the microbial agent, international travel, human susceptibility to infection, population growth, an aging population, climate and weather changes, and expanding vector habitats [2–5]. Four recent examples of disease emergences are the viral infections such as Chikungunya, Zika, Middle East Respiratory syndrome coronavirus (MERS-CoV), and the recently described novel coronavirus (COVID-19) infection, which represent new viral entities or viruses emergent in new geographic locales and characterized by novel complications [6–8]. However, the most important newest example of an emergent infectious disease is HIV infection, which emerged a century ago in a primate host(s), and subsequently spread within the human population.

Remarkable progress in our understanding of etiopathogenesis, natural course, diagnostics, and therapy (HAART) has occurred, which has led to a significant improvement in morbidity and mortality (9). To date, the status of a considerable proportion of HIV/AIDS patients has changed from a near fatal disorder secondary to opportunistic infections to a chronic disease in which cardiovascular, renal, diabetes, malignancy, and autoimmune co-morbid disorders have become prevalent and relevant [9–11]. The latter manifestations in which HIV-related rheumatic manifestations are included, make this topic of great relevance and importance to clinicians including rheumatologists and other practitioners dealing with this condition.

This review will attempt to define and discuss available data on HIV infection and rheumatic manifestations during the pre- and post-HAART eras.

1 Section of Rheumatology, Air Force Hospital, Aramburú Ave 2nd block, Lima, Peru
2 Louisiana State University Health Sciences Center, 433 Bolivar St, New Orleans, LA 70112, USA
Prevalence of rheumatic manifestations before the advent of highly active antiretroviral therapy

The prevalence of rheumatic manifestations among HIV-infected patients prior to the introduction of HAART ranged from 3 to 71% [12] and was associated with late stages of immunosuppression in HIV infection. And HIV-associated arthritis, reactive arthritis (ReA), psoriatic arthritis (PsA), painful articular syndrome, and diffuse infiltrative lymphocytosis syndrome (DILS) were the most commonly rheumatic disorders observed. In this pre-HAART era, the coexistence of HIV infection and systemic lupus erythematosus or rheumatoid arthritis was rarely observed given that these two diseases are CD4+ T cell–mediated process and HIV targets CD4+ T cell, therefore reducing the risk of development of these rheumatic diseases. After the introduction of HAART, rheumatic complications had a significant decline, including DILS, ReA, PsA, and myositis [13–15] (see Table 1).

Prevalence of rheumatic manifestations after the advent of HAART

Several prospective studies have conclusively shown that the prevalence of rheumatic manifestations associated to HIV infection has significantly declined in the HAART era, but of great interest and importance, a new group of rheumatic disorders has emerged covering the spectrum of systemic autoimmune and autoinflammatory diseases, posing a new clinical challenge [13–17] (see Table 2).

Walker-Bone et al. recently reported their experience with 363 HIV-positive patients, out of a cohort of 2042 HIV-infected patients (1837 (90%) male), with musculoskeletal manifestations seen between January 2005 and December 2012. Most (310, 85%) patients had no evidence of an underlying systemic inflammatory disorder but were diagnosed with regional musculoskeletal pain, specific soft tissue disorders, chronic widespread pain, or osteoarthritis. Among the remaining 53, only seronegative arthritides were present more often than would be expected for the general population [18].

There are few studies dealing with the incidence, prevalence, and chronology between rheumatic disorders associated with HIV infection and AIDS; however, two large studies, one from Taiwan and the second from France, merit discussion [19, 20]. In the first study, Yen et al. reported on the incidence of AIDS in a nation-wide HIV/AIDS patient (PLHWA) cohort in Taiwan and compared with the general population. An interesting observation was the lower risk for development of AS despite a high prevalence of HLA-B27 in Taiwanese people (5%). In contrast, PLHWA who received HAART had higher standardized incidence rates (SIRs) for psoriasis, AHA, and uveitis, while those that did not receive HAART had higher SIRs for Sjogren’s syndrome, psoriasis, RA, SLE, and other autoimmune disorders. Lebrun et al. also conducted an epidemiologic study in a French nation-wide HIV cohort to estimate the prevalence of inflammatory and autoimmune diseases (IADs) among patients living with HIV (PLHIV) in the HAART era (from January 2000 to July 2013), and to describe their occurrence according to HAART onset, the immune-virological status, and hepatitis C virus (HCV) and/or hepatitis B virus coinfection. Published reports showed that several IADs including psoriasis, sarcoidosis, RA, ankylosis spondylitis (AS), Graves’ disease, Hashimoto’s thyroiditis, autoimmune hemolytic anemia (AHA), immune thrombocytopenia, autoimmune hepatitis, myasthenia gravis (MG), Guillain-Barre syndrome (GBS), and chronic inflammatory bowel disease were the most prevalent diseases. Majority of patients (59%) developed IAD after HIV infection with a mean delay of 10.6 ± 6.4 years. In addition, in patients developing IAD after the diagnosis of HIV infection, 572 (70%) were on HAART and 419 of them (73%) had undetectable HIV viral load. Comparing data from the Taiwan and French studies, some geographical variability in terms of IADs is observed but both studies confirmed previous reports in the literature concerning the relationship between HIV/AIDS and rheumatic disorders.

Spondyloarthritis

Most reports in the pre-HAART era clearly demonstrated a worldwide increase in the prevalence of ReA, PsA, and to a lesser extent AS compared with the general population, although some differences were noted according to mode of transmission, geographic variation, and degree of immunosuppression. This was more striking for both psoriasis and PsA in sub-Saharan African countries in which the incidence and prevalence of both disorders were low despite the presence of the risk allele for psoriasis HLA-CW6. This, however, drastically changed following the advent of HIV in which both disorders were increasingly seen in African populations [12, 21–24]. A similar situation occurred in Asian populations in which both psoriasis and PsA were of low prevalence, only to increase following the HIV pandemic. Post-HAART, both psoriasis and PsA have diminished in Africa and Asia.

Rheumatoid arthritis

Early reports showed that patients with active rheumatoid arthritis (RA) became inactive following infection with VIH; however, this situation did not occur in all RA patients and erosive RA has been shown to develop even in RA patients who develop AIDS. Therefore, the assertion that AIDS might lead to remission in RA requires further investigation [25, 26].
On the other hand, the presence of low titer rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP) in patients with HIV may lead to an erroneous diagnosis of RA. HIV patients may also exhibit a high proportion of RF and CCP antibodies, which decrease after initiation of HAART suggesting that HIV is capable of inducing autoantibodies [27, 28].

Connective tissue disorders

Systemic lupus erythematosus

Overlapping clinical and laboratory presentations of SLE and HIV infection may give rise to diagnostic challenges; active SLE and HIV infection shared several manifestations such as fever, arthralgia, arthritis, myalgia, skin rash, lymph node enlargement, cytopenias, pulmonary, cardiovascular, renal and CNS involvement, ANAs, and anticardiolipin antibodies, but hypocomplementemia secondary to HIV has not been described, and this finding may be useful to distinguish lupus activity from HIV infection [29].

Decrease in CD4 lymphocytes might ameliorate SLE disease activity and induce remission. However, it is interesting to note that SLE disease activity may persist during HIV infection and not be related to the use of HAART demonstrating that CD4+ cells are not the only player in this immunodeficiency disease [30].

Two recently published reports highlight the association between HIV infection and SLE. Hax et al. described 11 patients exhibiting concomitant HIV and SLE in whom the most salient features were more neuropsychiatric lupus and smoking, and higher SLICC damage index as compared with SLE patients without HIV infection, although the survival rate was similar in both groups. In addition, anti-Sm antibody was found more prevalent in patients with SLE without HIV [31].

| Table 1 | HIV-associated rheumatic manifestations in the pre-and post-HAART era |
|---------|---------------------------------------------------------------|
| Rheumatic manifestation | Pre-HAART | Post-HAART |
| Intermittent painful articular syndrome | + | −/? |
| HIV-associated arthritis | ++ | −/? |
| Spondyloarthritis | | |
| - Reactive arthritis | ++ | −/+ |
| - Psoriatic arthritis | ++ | −/+ |
| Connective tissue disease | | |
| - SLE | −/+ | + |
| - RA | −/+ | + |
| - Polymyositis | + | − |
| - Vasculitis | + | − |
| - DILS | +++ | −/+ |
| Serological abnormalities | | |
| - Hypergammaglobulinemia | +++ | + |
| - Cryoglobulinemia | +++ | + |
| - Rheumatoid factor (RF) | ++++/++/+++ | + |
| - Anti-cyclic citrullinated peptide antibodies | + | −/+ |
| - Antinuclear antibody (ANA) (low titer) | ++ | + |
| - Anticardiolipin (aCL) (IgG) | ++++/++++ | + |
| - pANCA | + | ? |

Frequency of presentation:
Increased/decreased: +, low; ++, moderate; ++++, high; −, absent; ?, unclear

| Table 2 | Immune reconstitution inflammatory syndrome. Post-HAART era |
|---------|---------------------------------------------------------------|
| Rheumatic | Non-rheumatic |
| SLE/DLE | Pulmonary sarcoidosis |
| Polymyositis | Graves’ disease |
| Kawasaki disease | Hashimoto’s thyroiditis |
| Behcet disease | Multiple sclerosis |
| Rheumatoid arthritis | Guillain-Barre syndrome |
| Adult-onset Still’s disease | Myasthenia gravis |
| Autoimmune hepatitis | Autoimmune hemolytic anemia |
| Autoimmune thrombocytopenia | |
Naovarat et al. identified 22 patients with concomitant SLE and HIV infection in their cohort of HIV patients followed longitudinally over a 25-year period. Data is similar to that previously reported by Hax et al., although they showed that the prevalence of SLE was high in black HIV-infected women, and skin/mucosal involvement and DNA antibodies were less common in patients with concomitant HIV and SLE. Of interest, patients diagnosed with HIV infection after the advent of HAART tended to present with SLE in a shorter time than patients with HIV prior to the advent of HAART [32].

Anti-phospholipid syndrome

Circulating antiphospholipid antibodies, including anticardiolipin, lupus anticoagulant, and anti-B2-glycoprotein I, are a common occurrence in most HIV patients, but in general, their clinical significance is irrelevant. Only a handful of clinical cases have been reported [12, 31, 32].

Systemic sclerosis

The association between HIV infection and systemic sclerosis (SSc) is rare. The few cases reported in the literature do not allow for a meaningful analysis [33, 34].

Polymyositis and dermatomyositis

HIV-associated polymyositis usually has mild disease activity, which is often difficult to recognize, especially in a population that frequently presents generalized weakness and a debilitating course. Other causes of myopathy reported are high dose of zidovudine, statins-related, and nemaline myopathy [35].

Diffuse infiltrative lymphocytosis syndrome

Prior to HAART its prevalence used to be highest among African Americans (up to 48% of infected individuals) and associated with HLA class II alleles (DRB1) that is not seen in other racial groups with diffuse infiltrative lymphocytosis syndrome (DILS), and occurring in patients whose disease was at a less advanced stages. The syndrome usually presents as a Sjogren-like disease with sicca symptoms with bilateral parotid gland swelling, lymphadenopathy, and extra-glandular organ involvement. DILS is also characterized by CD8+ T cell infiltration, lack of autoantibodies (anti-Ro and anti-La), although they may be present in some exceptions, and extra-glandular visceral infiltration. The lung being the most common extra-glandular organ involved and when affected it presents as a lymphocytic interstitial pneumonitis (LIP) [36]. Its natural history has also changed since the introduction of HAART, and it is less frequently seen including the extra-glandular manifestations such as LIP.

Chen et al. showed in the Taiwanese population that the incident rate of DILS was 0.56/1000 person-years higher than in the general population, and the incidence was higher in patients without HAART than in patients with HAART, supporting the notion that HIV intervenes in the pathogenesis of DILS and that HAART reduces the risk of acquiring DILS [15, 19].

DILS patients with mild symptoms may not require specific treatment, but glucocorticoids or immunosuppressive drugs should be considered for patients with progressive glandular involvement.

Vasculitis

The incidence of vasculitis in HIV infection is relatively low 1%, and when present it can affect small, medium, and large size blood vessels. Its presence, however, varies according to ethnic origin, and it appears to have a higher prevalence in Orientals, and on the route of transmission. Vasculitis occurs more commonly in those with a profound state of immunosuppression (CD4+ < 200/mL), in association with hepatitis B infection, but has also been reported in the early stages (> 500/mL) [37]. Zhang et al. have reported a high prevalence of vasculitis when compared with other rheumatic syndromes [38]. A variety of syndromes have been reported including Takayasu arteritis, polyarteritis nodosa, Kawasaki-like syndrome, Behcet-like disease, Henoch-Schonlein purpura, digital gangrene, and central nervous system vasculitis [38–46]. In addition, serum cryoglobulins and ANCA antibodies, especially pANCA, are common, up to 40–50%, but their clinical significance is uncertain (43, 44). In the HAART era, HIV-infected patients have been shown to have decreased levels of serum cryoglobulins [44].

Septic arthritis

Contrary to what might be expected, osteoarticular infection due to pyogenic bacterial does not occur more frequently in patients with HIV infection, and published data reveals a relatively low risk for septic arthritis [13, 47]. However, it should be noted that there is a single study that reported a prevalence of infection of 20% [22]. Atypical microorganisms rarely occur except in advanced HIV infection. Atypical mycobacterium and fungal microorganisms occur in advanced HIV infection (CD4 count less than 100/mL).

Immune reconstitution inflammatory syndrome

Restoration of immune competence associated to suppression of virologic response following initiation of HAART might result in development of autoimmune disorders and
reactivation of underlying opportunistic infections. This constellation of events known as immune reconstitution inflammatory syndrome (IRIS) is linked to a rapidly recovering immune system, and it appears directly related to an increase in CD4+ T cells, CD8+ T cells, CD4+/CD8+ T cell ratio, and increased cytokine levels.

Calabrese et al. conducted a prospective, longitudinal cohort study and described 32 cases associated with IRIS including sarcoidosis, RA, and SLE [14].

IRIS may develop days to months after HAART begins, and most cases resolve spontaneously, but at times they can become life-threatening in severity, requiring therapeutic interventions. Generally, however, IRIS is a self-limiting process in which it is not necessary to discontinue HAART, and it should not require lifelong therapy [14, 48].

### Bone diseases (see Table 3)

#### Osteoporosis

As longevity in HIV-infected individuals increases, new comorbid conditions including osteopenia and osteoporosis, with their increase in the risk of bone fractures, develop. The estimated prevalence of osteoporosis in the HIV population is 15% and of osteopenia 52%. Bone density decreases between 2 and 6% during the first 2 years of HAART [49, 50], and the rate of fracture in the HIV population is between 30 and 70% compared with control non-HIV population [51–53].

In addition, to classic osteoporosis risk factors other HIV-specific risk factors such as low CD4+ cell count, coinfection with hepatitis C, and antiretroviral therapy may all contribute to the increase risk in osteoporosis [51, 52].

There is no specific guide for the assessment and management of HIV patients with decreased bone density; however, FRAX has been recommended for routine evaluation of fracture risk in PLWH despite the limited predictive value in these patients [54].

Management of osteoporosis in PLWH should follow the same recommendations for the HIV-negative population, an adequate nutrition including calcium and vitamin D and modification of lifestyles, pharmaceutical therapy with bisphosphonates, alendronate and zoledronic acid, have been shown to have a positive effect on BMD and tolerability similar to those found in the general population [54–57]. Currently, other therapeutic options have not been evaluated.

#### Avascular bone necrosis

Osteonecrosis (avascular bone necrosis, AVN) may occur at any joint, but when affects hips or any other large joint might eventually lead to severe disability. AVN might have a higher incidence than in the general population [58]. Its prevalence might be comparable to the prevalence reported in patients at high risk for osteonecrosis in the context of a variety of underlying diseases, i.e., glucocorticoid-induced AVN.

Its etiology and potential risk factors are poorly understood, and further studies are needed to have a better understanding of this complication [59].

### Table 3

|                      | Pre-HAART | Post-HAART |
|----------------------|-----------|------------|
| Osteonecrosis        | +         | ++         |
| Osteopenia/osteoporosis | +     | ++         |

#### Therapy of rheumatic disorders in HIV-infected patients

HIV infection has significantly impacted on the natural history and therapeutic intervention of autoimmune diseases due to the presence of underlying immunosuppression and that the use of immunosuppressive drugs or biologic agents may lead to serious complications including infections.

Management of autoimmune diseases (AIDs) is similar in HIV-positive and HIV-negative patients. Most patients afflicted with HIV-associated AIDs including inflammatory musculoskeletal involvement respond well to conventional therapy such as NSAIDs, narcotic drugs, and DMARDs, but refractory cases may need the use of biological agents, especially TNF inhibitors [60]. When considering immune suppressive therapy, it is important to keep in mind that CD4+ T cells are necessary in the control of intracellular and extracellular bacteria, parasites, and viruses [61].

At present, biologic agents and other DMARDs (including glucocorticoids, hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, mofetil mycophenolate, azathioprine, cyclophosphamide, cyclosporine) are recommended when patients have CD4+ T cell counts above 200 cells/mm³ and HIV viral activity completely suppressed [62–64]. In addition, they have been shown to be effective, safe, and well-tolerated. In certain situations, especially in lupus patients, treatment should be individualized and should be tailored at reaching a balance between HIV infection and lupus activity.

### Prophylaxis

General consensus suggests that prophylaxis against opportunistic infection should be given to all HIV patients on immunosuppressive therapy due to an increased risk of infection reactivation. Special attention should be given to the presence...
of tuberculosis (TB), varicella zoster, and opportunistic infections such as *Pneumocystis jirovecii* (PJ) [62, 65]. In addition, HIV patients should be screened for HBV, HVC, and other infections taking into considerations endemic geography [66]. Prophylaxis for TB should follow the CDC guidelines, although no guidelines for the prophylaxis of PJ in connective tissue disorders exist [67–69].

HIV patients on immunosuppressive therapy have an increased risk of infection reactivation. Close attention to the association between tuberculosis, varicella zoster, and opportunistic infections such as PJ should be kept in mind [62, 65]. Patients should be screened for HIV viral load, HBV, HVC, TB, and other infections according to endemic geography [66].

**Conclusion**

It can be concluded that following the introduction of HAART, there has been a decline in the incidence and prevalence of seronegative arthritides and certain autoimmune disorders including DILS, SLE, RA, and polymyositis, but certain systemic metabolic and inflammatory disorders, especially osteoporosis, avascular bone necrosis, immune reconstitution syndrome, sarcoidosis, autoimmune hemolytic anemia, Graves’ disease, psoriasis, immune thrombocytopenia, and inflammatory bowel disease have emerged. Glucocorticoids and other immunosuppressive agents appear to be effective and well-tolerated, and prophylaxis of infection is very important.

**Compliance with ethical standards**

**Disclosures** None.

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