

Review

Rheumatic conditions in human immunodeficiency virus infection

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Many rheumatic diseases have been observed in HIV-infected persons. We, therefore, conducted a comprehensive literature search in order to review the prevalence, presentation and pathogenesis of rheumatic manifestations in HIV-infected subjects. Articular conditions (arthralgia, arthritis and SpAs) are either caused by the HIV infection itself, triggered by adaptive changes in the immune system, or secondary to microbial infections. Muscular symptoms may result from rhabdomyolysis, myositis or from side-effects of highly active anti-retroviral therapy (HAART). Osseous complications include osteonecrosis, osteoporosis and osteomyelitis. Some conditions such as the diffuse infiltrative lymphocytosis syndrome and sarcoidosis affect multiple organ systems. SLE may be observed but may be difficult to differentiate from HIV infection. Some anti-retroviral agents can precipitate hyperuricaemia and are associated with arthralgia. When indicated, immunosuppressants and even anti-TNF- α agents can be used in the carefully monitored HIV patient. Thus, rheumatic diseases and asymptomatic immune phenomena remain prevalent in HIV-infected persons even after the widespread implementation of highly active anti-retroviral therapy.

KEY WORDS: Acquired immunodeficiency syndrome, Anti-retroviral therapy, Arthritis, Human immunodeficiency virus, Psoriasis, Rheumatic diseases, Vasculitis.

Introduction

HIV-infected individuals are at an increased risk of developing musculoskeletal pathology [1, 2]. Estimates of the exact prevalence of rheumatic manifestations of HIV infection vary widely. Before the widespread implementation of highly active anti-retroviral therapy (HAART), retrospective studies calculated the rates of musculoskeletal complications from 11% to 72% [3–5]. In the HAART era, rheumatic complications declined significantly but continue to be prevalent [6–8] with even new manifestations emerging [9]. The aim of this article is to review the rheumatic complications in HIV-infected subjects. An overview is provided in Table 1.

Laboratory abnormalities

In HIV-infected patients, autoimmune phenomena may be fostered by a polyclonal stimulation of B cells, or the homeostatic expansion of naïve and antigen-experienced T cells after the initiation of effective HAART [10]. Laboratory abnormalities may consist of the presence of RF, cold agglutinins or ANA [2, 5, 11–14]. Anti-centromere ANA were observed in up to 84% of individuals and circulating immune complexes in up to 98%. C3 and C4 complement levels were mostly normal, although in some subjects elevated or low levels were measured [5]. ANCA have been described at high frequency [14, 15].

Infections are a known trigger of aCL production [16]. In HIV-infected patients, aPLs were found in up to 94% of the cases and anti- β 2 glycoprotein I (GPI) antibodies in up to 47%. The lupus anti-coagulant was mostly negative [2, 16–19]. The full picture of the APS is uncommon [20–22], a fact which may be related to the relatively low prevalence of anti-GPI antibodies and the observation that aCLs are often transient and disappear with anti-retroviral treatment [16].

Arthralgia

Arthralgia is a common but unspecific complaint of HIV-infected persons. The prevalence of arthralgia in HIV-infected persons was 5% in retrospective and 45% in prospective studies [2, 3, 5]. Arthralgia was most frequently observed in the knees, shoulders and elbows [5]. An intermittent painful articular syndrome has only a short duration (a few hours), but may require opioid analgesics [23, 24].

Arthralgia is also common in acute HIV infection. Following an incubation period of a few days to a few weeks after HIV infection, 40–90% of the individuals present with a flu-like illness that includes joint pain in 28–54% of the cases. Other symptoms are fever (80–88%), rash (51–58%), oral ulcers (8–37%), myalgias (49–60%), pharyngitis (43%) and malaise (68–73%) [25, 26]. Fever and malaise are in fact the most sensitive symptoms for the diagnosis of primary HIV infection but rarely persist beyond 14 days [25]. The diagnosis of acute HIV-1 infection hinges on the presence of HIV-1 RNA in the absence of HIV-1 antibodies.

Arthritis

HIV-associated arthritis

Arthritis of different aetiology is described in 10–12% of the HIV patients [2, 5, 27, 28]. HIV-associated arthritis can present at any time during the course of chronic HIV infection; its prevalence was 1% in a tertiary care setting [8]. HIV-associated arthritis mainly manifests as a non-erosive oligoarthritis of the lower extremities without enthesopathy, mucocutaneous involvement and HLA-B27 gene expression [7, 27]. HIV was isolated from the SF in only one report [29]. Most frequently, HIV-associated arthritis is self-limited and lasts <6 weeks [27].

Reiter's syndrome

A SpA resembling ReA is more prevalent in HIV-positive paediatric and adult cohorts, compared with HIV-negative population [7]. Reiter's syndrome was diagnosed in 0.4–10% of the HIV-infected subjects, most of whom had asymmetric oligoarthritis [2, 5, 23, 27]. Enthesopathy is highly prevalent and sacroileitis may occur [5]. Among the extra-articular manifestations, conjunctivitis, circinate balanitis, urethritis and keratoderma blennorrhagicum are frequent [5]. HLA-B27 was positive in five of eight patients with

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TABLE 1. Overview of the rheumatic manifestations in the setting of HIV infection

Manifestation	Most important causes in the setting of HIV infection	Principal treatment
Arthralgia	Primary HIV infection Intermittent painful articular syndrome Indinavir, ritonavir, saquinavir Arthritis (see below)	Indication for temporally limited HAART controversial Analgesics Replace PI
Arthritis	HIV-associated arthritis Reactive arthritis Psoriasis Gout Septic (intravenous drug abuse) Cryoglobulinaemia	Symptomatic, consider indomethacin HAART, SSZ, TNF- α antagonists HAART, MTX, TNF- α antagonists HAART without stavudine and didanosine Antimicrobial HAART, IFN and ribavirin in HCV coinfection
Myalgia	Primary HIV infection Some statins if given with some PI	Symptomatic Switch statin and/or avoid PI
Rhabdomyolysis	Primary HIV infection Alcoholism, cocaine, other illicit drugs Statins in the setting of PI cotherapy Trimethoprim/sulphamethoxazole Tenofovir-induced macroglobulinaemia	Symptomatic Avoid precipitating agent Replace Replace Not a clinical problem
Muscle weakness	Zidovudine myopathy Polymyositis DILS Dermatomyositis Nemaline rod myopathy Wasting syndrome Pyomyositis	Uridine supplement, avoid zidovudine HAART HAART Unknown Prednisolone? Plasmapheresis? HAART Antimicrobial
Osteonecrosis	Corticosteroids PI controversial	Symptomatic
Osteopenia/osteoporosis	Multifactorial?	Eliminate cofactors (smoking), vitamin D, calcium, bisphosphonates
Osteomalacia	Tenofovir-induced hypophosphataemia	Replace tenofovir, phosphate supplementation
Osteomyelitis	<i>Staphylococcus aureus</i> and other organisms	Anti-microbial treatment
Vasculitis	PAN Hypersensitivity vasculitis Cryoglobulinaemia Behçet's-like disease Aneurysmatic or obstructive large-vessel vasculitis Cerebral vasculitis Vasculitic manifestations due to lymphoma Infections (varicella zoster, CMV)	HAART, treatment of HBV coinfection HAART, corticosteroids, immunosuppression HAART, IFN plus ribavirin in HCV coinfection Unknown Rule out lues, treatment unknown Unknown Chemotherapy Anti-viral HAART
DILS	Must be differentiated from SS, HCV, <i>Pneumocystis jirovecii</i> pneumonia and sarcoidosis	
Sarcoidosis	Unknown	Corticosteroids
Parotid lipomatosis	Ritonavir	Avoid ritonavir doses exceeding 200 mg/day
SLE	Unknown	HCO, immunosuppression

HIV-associated Reiter's syndrome [5]. SSZ has been successfully used. Dramatic improvement with effective HIV suppression or anti-TNF- α biologics was described [30, 31].

Psoriasis and PsA

The incidence of PsA is ~1.5–2% [5, 23, 27]. In general, the severity of psoriasis parallels the impairment of the immune system and the use of anti-retrovirals generally improves HIV-associated psoriasis. In advanced HIV infection, psoriasis can be generalized and extremely resistant to therapy. Anti-TNF- α agents have been successfully administered to a few patients [32, 33], but in some cases have been associated with polymicrobial infections [34].

Septic arthritis

Immunodeficiency is a risk factor for septic arthritis [7, 35]; septic tenosynovitis and bursitis have been less often described [36]. Although the joints are the most common localization of septic complications in the musculoskeletal system [37, 38], these infections are only observed in ~1% of HIV-infected individuals [37, 39]. The largest studies retrospectively identified 14–30 cases of musculoskeletal infections among cohorts of 3000–4000 patients [37, 39]. There appears to be no clear association with CD4+ counts [39]. Some studies, however, question whether HIV infection actually predisposes for articular infections and suggest that the predominant risk factor for septic arthritis in the HIV-infected population is represented by simultaneous intravenous drug abuse [39, 40].

Septic arthritis usually affects young men, with the large weight-bearing joints of the lower extremities commonly involved [39]. For unclear reasons, the sternoclavicular joints are a preferred target of infection in intravenous drug users [41]. Pyogenic organisms predominate at CD4+ counts >250/ μ l, whereas opportunistic pathogens are observed when the CD4+ counts are <100/ μ l [39]. After the initiation of HAART, pre-existing opportunistic pathogens such as mycobacteria can become symptomatic by immune reconstitution.

Articular complications of anti-retroviral therapy

Arthralgia, monoarthritis [42], oligoarthritis [43] and adhesive capsulitis [44] have been associated specifically with the use of indinavir. Indinavir is an anti-retroviral protease inhibitor (PI), which tends to form drug crystals in the urogenital tract, giving rise to nephrolithiasis. Indinavir crystals were not detected in the SF, however [42]. Indinavir is now rarely used in HAART for its unfavourable pharmacokinetic profile, efficacy and side-effects [45, 46]. A prospective survey suggested that joint pain may also be associated with other PI (ritonavir and saquinavir) [47].

Gout

High frequencies of hyperuricaemia (up to 42%) have been observed in HIV-infected individuals [2, 48, 49]. In HIV patients, the annual incidence of gout is 0.5%, an order of magnitude higher than the incidence in the normal population [50–52].

With uncontrolled HIV replication, serum urate elevation may result from increased cell turnover [49, 53]. Aside from the HIV

infection itself, urate serum levels are also altered by anti-retrovirals [54]. Didanosine, for example, causes hyperuricaemia [55] and urate measurements were even proposed as an index of drug compliance [56]. In a recent multivariate cohort analysis, hyperuricaemia was associated with factors previously identified in HIV-uninfected individuals, but in addition with the use of some anti-retrovirals, particularly with stavudine and didanosine [54]. Urate elevation may result from the mitochondrial toxicity of these drugs, because mitochondrial damage increases the formation of lactate, which stimulates urate reabsorption at the proximal tubulus of the kidney [57]. Mitochondrial failure also causes ATP depletion that promotes urate production in the purine nucleotide cycle [58].

Myopathy

Muscular complications associated with HIV consist of rhabdomyolysis, zidovudine myopathy [59–61], an HIV-associated polymyositis [23, 62–67], dermatomyositis [68], inclusion body myositis [69, 70], nemaline rod myopathy [66, 67], wasting syndrome [71, 72] and pyomyositis [37, 38, 73, 74].

Rhabdomyolysis

Rhabdomyolysis may either complicate primary HIV infection [75, 76], result from the use of the interaction between PI and statins or be due to other drugs [77–79]. A hypersensitivity reaction to abacavir, for example, has triggered rhabdomyolysis [80]. Rhabdomyolysis and more frequently *myalgia* may be induced in patients who receive lipid-lowering agents to counteract dyslipidaemia as a common side-effect of HAART. These complications result from significantly elevated statin concentrations in the serum due to the shared metabolism of statins and PI at hepatic cytochrome P 450 isoenzymes [81–84]. Lovastatin and simvastatin, in particular, should be avoided with PI co-treatment and pravastatin considered the cholesterol-lowering agent of choice [85]. Atorvastatin may also be used with caution but should be used as a second-line agent [83, 85].

The formation of a macroenzyme CK has been observed in approximately half of the patients treated with tenofovir [86]. Macro CK should be suspected with a disproportional elevated MB isoenzyme activity and does not reflect a clinically significant cardiac or skeletal myopathy.

Zidovudine

Zidovudine causes a myopathy by interfering with the replication of mitochondrial DNA [59, 60]. The myopathy is probably specific to zidovudine because it is generally not observed under treatment with other anti-retroviral nucleoside analogues [60, 87]. Zidovudine myopathy is probably the most frequent muscle complication in HIV patients and also more common than the inherited mitochondrial myopathies due to mutations in the mitochondrial genome [88]. Patients experience muscle weakness either under dynamic or static exercise [89]. The serum CK is often normal or only minimally elevated [89] but muscle histology reveals a high frequency of ragged-red fibres in the Gomori Trichrome stain. By histochemistry and electron microscopy a high frequency of cytochrome c-oxidase negative fibres harbouring abnormal mitochondria are found. Zidovudine myopathy may be prevented by uridine supplementation and resolves within months after drug cessation [60, 90].

HIV-associated polymyositis

This has been described in up to 2–7% of HIV-positive patients and can be observed at any stage during the course of the infection [5, 23, 62]. In a prospective trial of consecutive HIV-infected patients untreated with anti-retrovirals but clinically suspected skeletal myopathy or raised serum CK levels, one-third of the

cases had an inflammatory condition on skeletal muscle biopsy (microvasculitis, myositis) [91]. The muscle is typically infiltrated by CD8+ T-lymphocytes [65]. Viral antigen and nucleic acids have been detected in endomysial lymphocytes [63, 64]. HIV-associated polymyositis is clinically and histologically indistinguishable from idiopathic polymyositis but mostly has a good outcome as it responds well to immunosuppressive therapy and may even resolve spontaneously [62]. About half of the patients simultaneously have a diffuse infiltrative lymphocytosis syndrome (DILS) [62, 92].

Dermatomyositis and inclusion body myositis

Dermatomyositis [68] and inclusion body myositis were observed with HIV infection only rarely [69, 70]. In inclusion body myositis, HIV-specific CD8+ T cells appear to recognize antigens on the surface of muscle fibres [70].

Nemaline rod myopathy

A nemaline rod myopathy of adult onset is also rare. Patients progressively develop a painless muscle weakness and wasting with elevated serum CK [66, 67]. Muscle biopsy discloses atrophic type I fibres carrying numerous intracytoplasmic nemaline rod bodies, whereas necrotic fibres and inflammatory infiltrates are not features of the disease. Despite the absence of muscle inflammation, some patients may respond to prednisolone or plasmapheresis, which suggests an autoimmune mechanism [93, 94].

Severe muscle atrophy may be caused by the AIDS-defining ‘wasting syndrome’ that is characterized by an involuntary weight loss of at least 10% of body weight due to persistent diarrhoea, weakness or fever without concurrent illness. Where anti-retroviral treatment is available, wasting has become rare [71]. Muscle biopsy usually reveals diffuse, or type II fibre atrophy, mild neurogenic atrophy or thick filament loss without inflammation [72].

Pyomyositis

Pyomyositis is also a rare microbial infection, which mainly affects male patients with low CD4+ counts [37]. *Staphylococcus aureus* is the agent most frequently isolated [37, 38, 73, 74] but many other organisms have also been identified.

Bone complications

Osteonecrosis

HIV-infected patients have an ~100-fold elevated risk of osteonecrosis compared with the general population. At the hip, which is the most frequent localization of osteonecrosis, the prevalence was estimated as 4.4% by MRI [95]. The annual incidences were 0.7 and 0.3% with regard to asymptomatic and symptomatic osteonecrosis of the femoral head [96]. Hip osteonecrosis is frequently bilateral and may also be associated with avascular necrosis of other bones. Eleven percent of initially asymptomatic patients eventually require hip replacement [96]. Chronic inflammation, corticosteroids in the setting of immune reconstitution and aCLs have been suggested as risk factor by some but not all studies [95–99]. Osteonecrosis was attributed to hypertriglyceridaemia secondary to PI treatment, but other studies could not confirm the association of PI and osteonecrosis [95, 98].

Bone mineral loss

Osteopenia and osteoporosis are highly prevalent among HIV-infected patients. The loss of bone minerals is of multifactorial origin [100]. HIV-mediated immune activation and cytokine release contribute [101]. PI treatment was implicated in cross-sectional studies [102] but later refuted in longitudinal studies [101, 103]. It has been demonstrated that bisphosphonates increase bone mass density also in HIV-infected individuals

[104, 105] but it is not known if HIV-associated osteopenia actually increases the risk of bone fractures [106]. Thus, it is unclear if fractures can be prevented by bisphosphonates in the setting of HIV infection.

Osteomalacia

Symptomatic osteomalacia due to tenofovir nephrotoxicity has been described [107, 108]. Tenofovir probably inhibits the replication of mitochondrial DNA in the proximal tubules of the kidney and through this mechanism induces a Fanconi syndrome with tubular phosphate loss [109]. Osteomalacia should be suspected with hypophosphatemia and elevated alkaline phosphatase. Skeletal scintigraphy may reveal pseudofractures (Looser's zones) that are not evident in routine radiographs. The symptoms of osteomalacia improve during the course of a few weeks when tenofovir is discontinued and the phosphate substituted.

Osteomyelitis

Bone infections tend to occur at lower CD4+ counts than joint infections. *Staphylococcus aureus* is the most frequent pathogen [37, 39, 110] but polymicrobial infections are observed in a considerable proportion of HIV-associated osteomyelitis [110].

Multisystem manifestations

Vasculitis

A wide range of vasculitic manifestations were reported in HIV-infected individuals. Vasculitis was described early in the disease with CD4 counts $>500/\mu\text{l}$, and in severe immune-compromised patients with CD4 counts $<200/\mu\text{l}$ [111]. Vascular inflammation was looked for in 148 muscle, nerve or skin biopsies of symptomatic HIV-infected patients and found in 34 subjects [112]. Using the ACR 1990 classification criteria, four patients were classified as having PAN, one as having HSP and six as having drug-induced hypersensitivity vasculitis [112]. The majority of patients, however, had unspecific neutrophilic or monocytic vascular inflammation and heterogenous clinical features that included cutaneous rash, peripheral neuropathy or both [112].

Cryoglobulins (types II and III) were found in 1–27% of HIV-monoinfected, but far more frequently in HIV/HCV-co-infected patients [113–116]. Cryoglobulinaemic individuals appear to have lower C3 levels than their cryoglobulin-negative counterparts, but an association with HIV-viral load and CD4+ count is not evident [114–116]. Symptomatic cryoglobulinaemia may present with palpable purpura, mononeuritis, multiplex, arthralgias and nephrotic range proteinuria [115, 117], but in the majority of HIV-monoinfected patients, cryoglobulinaemia remains asymptomatic [114, 116, 118]. The prevalence of cryoglobulinaemia among HIV-positive/HCV-negative patients declines in the HAART era [119]. In the setting of HIV/HCV-co-infection, sustained clinical remission of cryoglobulinaemia can usually be achieved with IFN and ribavirin [117].

Among the vasculitides affecting the medium-sized arteries, cases of HIV-associated polyarteritis nodosa were observed [112, 120]. HIV antigens and HIV RNA were observed in the vessels in the absence of hepatitis B surface antigen [112, 120]. Behçet's disease has been described sporadically in HIV-infected patients [121]. A recent report from a tertiary hospital in China pointed out that ~15% of HIV-infected patients had a Behçet's-like disease, defined with at least three of the following features: oral and genital ulcerations recurring at least three times in a 12-month period, typical eye and skin lesions and a negative pathergy test [8].

Vasculitic complications of larger arteries in HIV-infected patients include coronaritis [122] and a large-vessel vasculitis with multiple aneurysms in African patients [123]. While some patients with occlusive or aneurysmatic large vessel involvement have an

infectious cause, others have a leucocytoclastic vasculitis of the vasa vasora and periadventitial vessels [124, 125].

Among HIV-infected patients with stroke, vasculitis was identified as the cause in 13% of individuals [126]. Cerebral vasculitis can occur immediately after HIV infection or in more advanced disease with CD4 counts $<200/\mu\text{l}$ [127, 128]. Granulomatous angiitis of the central nervous system (CNS) was found to even precede HIV seroconversion [129]. This condition is not specific to HIV and can be seen when the immune system is compromised for any reason [124]. It should, however, be borne in mind that CNS vasculitis with HIV infection may also be triggered by opportunistic infections with varicella zoster or CMV or be due to lymphoma [127]. Granulomatous necrotizing vasculitis was also observed outside the CNS in one case and then found to respond to anti-retroviral treatment [130].

DILS

DILS is a common problem in HIV-infected patients; the prevalence of DILS in this population is ~3% [131]. DILS may be confused with SS because DILS also presents with bilateral painless parotid gland enlargement, lacrimal gland enlargement and sicca symptoms [131]. DILS is characterized by circulating CD8+ lymphocytosis and antigen-driven CD8+ T cell infiltration of multiple organs. The condition usually manifests several years after HIV-seroconversion and is thought to reflect an excessive host response to HIV [132, 133]. Extraglandular complications consist of lymphoid interstitial pneumonitis (31%), muscular (26%) and hepatic (23%) involvement [62, 134]. Muscle manifestations are indistinguishable from polymyositis [92, 134]. A disproportionately greater degree of salivary gland enlargement and extraglandular disease, the low frequency of autoantibodies and RF, and the association with HLA-DR5 and -DRB1 distinguish DILS from SS [133, 135]. Anti-retroviral therapy is effective and probably also accounts for the declining incidence of DILS in the HAART era [135].

Parotid lipomatosis, a parotid gland swelling due to abnormal fat deposition was associated with PI therapy [136] and may represent a metabolic complication of high doses of ritonavir. These doses are no longer applied today. Gallium scans may distinguish parotid lipomatosis from DILS, the latter featuring an intense, bilateral salivary gland gallium uptake [137].

Sarcoidosis

The association of HIV and sarcoidosis was considered rare because CD4+ lymphocytes appear to play an important role in granuloma formation [138, 139]. In only few patients, sarcoidosis occurred in the absence of HAART [140, 141]. Although HIV-negative patients with sarcoidosis have also a decrease in peripheral blood T lymphocytes, a phenomenon which can be explained at least in part by the recruitment of T lymphocytes from the blood to the site of active granuloma formation, most patients with symptomatic sarcoidosis in the context of HIV infection had peripheral CD4+ lymphocyte counts $>200/\mu\text{l}$ [142]. Sarcoidosis is now mostly observed in patients with marked increases in CD4+ cell counts under HAART [9, 138, 140]. In the setting of such immune reconstitution, the interval between the introduction of HAART and the onset of pulmonary sarcoidosis was longer (several months) than that reported for granuloma formation secondary to infections (a few weeks) [140, 143]. Infections with pneumocystis jirovecii, cryptococcus, toxoplasma, CMV and mycobacteria must be excluded. In the HAART era, most patients with sarcoidosis showed improvement with immunosuppression and one with discontinuation of HAART [141].

SLE

SLE generally improves during the course of untreated HIV infection, which is consistent with the importance of CD4+ T cells

in the pathogenesis of SLE [144, 145]. Conversely, inactive pre-existing SLE can flare with immune recovery under HAART [9, 146]. Difficulties in the differential diagnosis between SLE and HIV infection may arise, because there are many clinical and laboratory similarities. For example, oral ulcerations, sicca syndrome, alopecia, arthritis, fever and neuropathies can be features of both conditions. Similarly, both entities can be accompanied by leucopenia, lymphopenia, thrombopenia, hypergammaglobulinaemia, ANA and the presence of aPLs [13, 147, 148]. Anti-dsDNA antibodies, are considered by some but not all investigators to be specific for SLE [12, 148]. Anti-HIV antibody tests can be falsely positive in SLE because sera from SLE patients contain antibodies that interact with HIV in western blot analyses [149–151]. Thus, positive HIV-antibody tests should be confirmed by antigen or nucleic acid detection in the setting of a CTD. It has also been described that the HIV infection emerged and took a rapidly progressive course after immunosuppressive therapy was initiated in order to treat SLE [147]. For this reason, it strongly recommended that subjects with SLE be tested for HIV prior to the commencement of immunosuppressive treatment.

Anti-rheumatics in HIV-infected individuals

For symptomatic relief of musculoskeletal symptoms, NSAIDs can be used according to the guidelines in HIV-negative patients. Interestingly, indomethacin has been shown to inhibit HIV replication *in vitro*, with the dose for 50% inhibition of viral replication corresponding to 50 mg of indomethacin [152]. Indomethacin may, therefore, be the NSAID to be preferentially considered in HIV patients. SSZ has been used successfully in SpAs not sufficiently responding to NSAIDs and does not adversely promote HIV replication [153, 154]. Although MTX was initially viewed as contraindicated in the setting of HIV infection because of its immunosuppressive mechanism of action, MTX may be used with careful monitoring of HIV viral loads and CD4 counts [155, 156]. HCQ has been effectively used in HIV-associated arthropathies [157]. Moreover, HCQ has anti-retroviral activity [158]. In a dose of 800 mg/day, HCQ was equal to zidovudine in controlling viral replication in HIV-infected patients [159, 160]. The anti-retroviral effect of HCQ was, however, only investigated for a daily dose of 800 mg of HCQ, a dose that is far more than the dose usually used to treat arthritis.

SpAs not responding to conventional DMARDs may require TNF- α blockade. Exogenous TNF- α was found to enhance HIV replication in a number of cell lines, which indicates that anti TNF- α biologics may have a beneficial effect on the course of HIV infection [161]. Such anti-retroviral action of TNF- α antagonists has, however, not been confirmed clinically; two consecutive infusions of infliximab were, however, well tolerated in six HIV patients with CD4+ counts <200/ μ l [162]. Good responses without severe side-effects were reported in cases of Reiter's syndrome, PsA and AS [31, 33, 163]. In some patients, however, the TNF- α agent had to be stopped despite efficacy due to intercurrent infections [34]. In a recent series of eight HIV patients treated with infliximab, etanercept or adalimumab, no deterioration due to HIV disease was observed during a mean observation period of 28 months [163]. Anti-TNF- α agents may also be safely used in the setting of hepatitis B and C virus coinfection [164, 165].

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Rheumatology key messages

- HIV infection can underlie autoimmune diseases.
- DMARDs can be used in HIV patients with autoimmune diseases.
- Prospective data about the incidence of rheumatic conditions in HIV patients are needed.

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