

ARTICULAR SYNDROMES IN ASSOCIATION WITH HIV INFECTION

Although articular manifestations as a result of HIV infection, apart from arthralgia, are uncommon, they may result in considerable morbidity.

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According to the UNAIDS Global Report there were 33.3 million adults and children with HIV at the end of 2009, and of them 22.5 million were living in sub-Saharan Africa. A total of 5 254 000 were receiving antiretroviral therapy and, of these, 971 556 were in South Africa. Thus, although articular manifestations due to HIV infection and the use of antiretroviral therapy are relatively uncommon, they may result in considerable morbidity in view of the large number of people who are at risk. The rheumatological manifestations of HIV have been the subject of many excellent reviews.¹⁻⁷

In Africa, the HIV epidemic was associated with an increase in the prevalence of reactive arthritis, psoriatic arthritis and undifferentiated spondyloarthropathy, all of which were previously uncommon, possibly as a result of the low background prevalence of HLA B27.

Since the first descriptions of psoriatic arthritis (1985) and reactive arthritis (1987) a variety of articular syndromes have been reported in association with HIV infection. The earlier reports from the USA and Europe described series of patients who were mainly homosexuals or intravenous drug users. These observations were followed by reports of articular manifestations in heterosexual HIV-positive patients from Africa.

The pattern of reactive arthritis reported among HIV-positive Caucasians in earlier studies was similar to the findings seen in those without HIV infection. However, in Africa the HIV epidemic was associated with an increase in the prevalence of reactive arthritis, psoriatic arthritis and undifferentiated spondyloarthropathy, all of which were previously uncommon, possibly as a result of the low background prevalence of HLA B27.⁸⁻¹⁰

In Europe and the USA the long-term use of antiretroviral therapy has been associated with a change in the spectrum of rheumatological manifestations. Recent reports describe newer manifestations occurring as part of the immune reconstitution inflammatory

syndrome (IRIS) and as a result of the adverse effects of antiretroviral therapy. An awareness of these manifestations is essential with the increased use of antiretrovirals in South Africa.

Spectrum of articular manifestations in association with HIV infection

The spectrum of articular manifestations reported in association with HIV infection is shown in Table I.

Table I. Articular syndromes associated with HIV infection

- Arthralgia
- Painful articular syndrome
- Spondyloarthropathies (SpA)
 - Reactive arthritis (Reiter's syndrome)
 - Psoriatic arthritis
 - Undifferentiated SpA
- HIV-associated arthritis
- Septic arthritis
- Osteonecrosis (avascular necrosis)
- Hyperuricaemia and gout

Arthralgia

Arthralgia is a common manifestation of HIV infection and its prevalence ranges from 5% of patients in retrospective studies to 45% in prospective studies. A higher prevalence is also encountered in longitudinal studies compared with cross-sectional studies. It may occur at any stage of the HIV infection. It is frequently oligoarticular but may also be polyarticular. It may be intermittent or persistent, and the intensity is usually mild to moderate. The joints most commonly involved are the knees, shoulders and the elbows. It responds to symptomatic treatment with analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), and usually settles with the use of antiretroviral therapy.

Arthralgia is a common manifestation of HIV infection and its prevalence ranges from 5% of patients in retrospective studies to 45% in prospective studies.

Painful articular syndrome

A distinct painful articular syndrome was reported in earlier studies but is now uncommon with the use of antiretroviral therapy. Patients experienced severe articular pain of short duration, ranging from a few hours to 24 hours. It was not associated with any signs of inflammation and responded to analgesics.

The SpA have been reported as one of the commonest manifestations of HIV infection and include reactive arthritis/Reiter's syndrome, psoriatic arthritis and undifferentiated SpA.

Spondyloarthropathies (SpA)

The SpA have been reported as one of the commonest manifestations of HIV infection and include reactive arthritis/Reiter's syndrome, psoriatic arthritis and undifferentiated SpA. Studies among Caucasians have been associated with a positive HLA B27 in 70 - 80% of patients while the HLA B27 is usually negative in studies from Africa. The joint manifestations may occur at any stage of the disease. Treatment with antiretroviral therapy has been shown to ameliorate the symptoms of SpA in many of the patients.

Reactive arthritis (Reiter's syndrome)

The clinical findings in these patients are similar to those encountered in HIV-negative patients. A history of a preceding urogenital or gastrointestinal infection is frequently obtained. Patients usually present with an asymmetrical oligoarthritis affecting predominantly the lower limbs. They may also have an enthesitis which may manifest as Achille's tendinitis, plantar fasciitis or tenderness at other enthesal sites. Axial involvement with inflammatory back pain and sacroiliitis is uncommon. Mucocutaneous manifestations include the presence of circinate balanitis and keratoderma blenorrhagica.

Reactive arthritis is uncommon in African blacks even though urogenital infections are frequently seen. However, reports from many countries in Africa have recorded an increased number of patients with reactive arthritis in association with HIV infection. Nearly all of these patients were HLA B27-negative.⁸

HIV-associated arthritis represents a larger proportion of patients with inflammatory arthritis in Africa.

Psoriatic arthritis

Psoriatic arthritis tends to occur more often with advanced HIV infection. Patients may present with extensive generalised skin lesions with a guttate-plaque type admixture. It is difficult to treat but may respond to antiretroviral therapy. In Zambia, 27 of 28 patients with psoriatic arthritis were found to be HIV-positive.⁹ The arthritis is often polyarticular with predominant involvement of the lower limbs (Fig. 1).

Undifferentiated spondyloarthropathies

Many patients may show some of the features of a SpA (according to the European Spondyloarthropathy Study Group (ESSG) preliminary criteria for the classification of a spondyloarthropathy),¹¹ but do not have all the features to permit a diagnosis of psoriatic arthritis, reactive arthritis or ankylosing spondylitis. These patients are classified as having an undifferentiated SpA and may represent the most common form of SpA seen in association with HIV infection.¹⁰ They may present with asymmetrical arthritis involving the lower limbs together with enthesopathy.

HIV-associated arthritis (Fig. 2)

Patients with an inflammatory arthritis who do not fulfil the criteria for an SpA and in whom the HLA B27 and serological tests such as



Fig. 1. Psoriatic arthritis in association with HIV infection – there is extensive psoriasis with involvement of the nails and deformities of the fingers.



Fig. 2. The hand of a patient with HIV-associated arthritis resembling rheumatoid arthritis with swelling of the proximal interphalangeal joints and the presence of early boutonniere deformities.

antinuclear factor, rheumatoid factor and anti-CCP antibodies are negative, are classified as having HIV-associated arthritis. Earlier studies from the USA and Europe noted that these patients usually accounted for about 10% of patients and they had an oligoarticular form of arthritis with predominant involvement of the lower limbs. The synovial fluid was reported to be non-inflammatory. The disease was to be self-limiting. A recent study in Congo Brazzaville reported 220 patients with HIV and rheumatological manifestations and found that 158 (71.8%) of their patients had HIV-related arthritis and 83.5%

of these patients had polyarthritis, which was symmetrical in 97.5%.¹² The symptoms of the majority of these patients resolved with NSAIDs in 2 - 5 weeks. HIV-associated arthritis represents a larger proportion of patients with inflammatory arthritis in Africa.

However, in our own experience and reports from Africa, a polyarticular pattern of presentation sometimes resembling rheumatoid arthritis is not uncommon. Some of the patients may have severe inflammatory arthritis with persistent disease which can result in joint destruction.

There are numerous reports on the occurrence of osteonecrosis (ON) of the hip in patients with HIV infection with or without antiretroviral therapy.

Septic arthritis

Initial studies in Europe and the USA noted that the major risk factor for the development of septic arthritis in HIV-positive patients was related to the intravenous drug abuse, rather than the HIV infection itself. The most common organisms were *Staphylococcus aureus* and the Streptococcal species. Infections with unusual organisms such as the fungal species and atypical mycobacteria usually occurred late in the course of the disease when the CD4 count was less than 100/mm³. However, the risk for septic arthritis may be increased in developing countries. The increased risk may be related to the lack of universal access to antiretroviral therapy and as a result many patients have advanced AIDS with very low CD4 counts.

Osteonecrosis (avascular necrosis)

There are numerous reports on the occurrence of osteonecrosis (ON) of the hip in patients with HIV infection with or without antiretroviral therapy. Some of the factors which might be expected to contribute to the development of ON are the use of corticosteroids, HIV-related vasculitis, protein S deficiency, antiphospholipid antibodies, antiretroviral therapy, especially protease inhibitors and hyperlipidaemia, which may also be related to antiretroviral therapy. These factors, together with alcohol abuse and severe immunosuppression associated with HIV infection, have been identified in small case series.

ON of the hip was reported in 104 (0.18%) of 56 393 HIV-positive patients in France¹³ and in 11 (1.1%) of 967 patients in Taiwan.¹⁴ The use of antiretroviral therapy was a strong risk factor in both these studies and the risk for ON increased from a relative risk of 2.6 for patients who received less than 12 months' treatment to a relative risk of 5.1 for patients on treatment for more than 60 months. However, it is difficult to determine the contribution of antiretroviral therapy in individual patients in whom other risk factors may also be present.

Hyperuricaemia and gout

Hyperuricaemia is frequently detected in patients with HIV infection. However, the development of gout is uncommon and only a few cases have been reported. Apart from the usual risk factors in HIV-negative patients, a rise in the uric acid may be related to increased cell turnover associated with uncontrolled viral replication or the use of antiretroviral drugs, especially didanosine and stavudine.

Immune reconstitution inflammatory syndrome (IRIS)

An IRIS with exacerbation of autoinflammatory or autoimmune diseases can occur with the successful treatment of HIV with antiretroviral therapy.^{1,5} Most autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and polymyositis occur *de novo* during IRIS, while in about 20% of cases there is a flare of the disease which was quiescent during the immunosuppression from HIV infection. Other organ-specific autoimmune diseases which may manifest include autoimmune thyroiditis and pulmonary sarcoidosis.

The time from the initiation of highly active antiretroviral therapy (HAART) to the onset of IRIS is about 9 months. Treatment with antiretroviral therapy is usually continued unless there is involvement of the eye or the central nervous system.

Arthritis in children

Arthritis associated with HIV infection also occurs in children, although it is reported less frequently than in adults. A series of 35 children with arthritis and HIV infection and 97 HIV-uninfected children with juvenile idiopathic arthritis was reported from Durban.¹⁵ Arthritis was the presenting manifestation of HIV infection in 78% of the children. When compared with children with juvenile idiopathic arthritis, the HIV-infected children showed a greater male-to-female ratio of 2.5:1, systemic-onset arthritis was not seen and spondyloarthropathy features were present in 34% compared with 5% for uninfected children. There was no difference in the prevalence of patients with oligoarthritis and polyarthritis.

Treatment of arthritis in patients with HIV infection

The initial management of the arthritis involves the use of non-pharmacological measures as for HIV-negative patients. Symptomatic relief is obtained with the use of analgesics and NSAIDs. Indomethacin inhibits HIV replication *in vitro*, and may therefore be the preferred NSAID in these patients. Chloroquine has antiretroviral activity in doses which are much larger than conventionally used for patients with arthritis. It is also effective in some patients with persistent arthritis. Salazopyrine can also be used safely as it does not promote viral replication and can be associated with an increase in the CD4 count.¹

An IRIS with exacerbation of autoinflammatory or autoimmune diseases can occur with the successful treatment of HIV with antiretroviral therapy.

Immunosuppressive agents must be used with extreme caution. A recent report of rapid progression of HIV in a patient with SLE who was treated with cyclophosphamide emphasises the need for caution. Methotrexate is also used with caution because of concern that it can promote viral replication due to its immunosuppressive properties. It has been used for inflammatory arthritis depending on whether patients are on concomitant antiretroviral therapy, the level of the CD4 count and the viral load. There are no defined protocols for its use, and careful monitoring is essential. Some patients with arthritis which is refractory to conventional disease-modifying anti-rheumatic drugs (DMARDs) have also been treated with anti-TNF agents but these should be reserved for use by clinicians familiar with their use and monitoring in this setting.

Many patients show an excellent response to antiretroviral therapy, and therapy should be initiated in patients who fulfil local guidelines. Some patients who have refractory arthritis and CD4 counts above 200/mm³ may also respond to antiretroviral therapy, but there are no clear guidelines for their use.

Other rheumatological manifestations associated with HIV infection

Apart from the various articular manifestations, which have been the focus of this review, a variety of other rheumatological manifestations have been reported in association with HIV infection and they are shown in Table II.¹⁻⁵

The diffuse infiltrative lymphocytosis (DILS) is characterised by bilateral enlargement of the parotid, submandibular and lacrimal glands. It is reported in 3 - 4 % of patients with HIV. Patients experience

Table II. Other rheumatological manifestations associated with HIV infection

- Muscle diseases – rhabdomyolysis, zidovudine myopathy, polymyositis, dermatomyositis, pyomyositis, nemaline rod myopathy
- Bone – osteoporosis, osteomalacia, osteomyelitis
- Vasculitis – polyarteritis nodosa, Henoch-Schönlein purpura, large-vessel vasculitis
- Diffuse infiltrative lymphocytosis syndrome (DILS)
- Immune reconstitution inflammatory syndrome – rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis
- Auto-antibodies – antinuclear factor, antiphospholipid antibodies, antineutrophil cytoplasmic antibodies (ANCA), anti-CCP antibodies, rheumatoid factor

Table III. Rheumatological manifestations associated with antiretroviral therapy

- Myopathy – associated with zidovudine and nucleoside analog reverse transcriptase inhibitors
- Rhabdomyolysis – reported in patients on protease inhibitors, especially in association with statins
- Cutaneous vasculitis – reported in association with zidovudine and didanosine
- Hyperuricaemia – reported with didanosine and stavudine, and gout has been reported with ritonavir
- Osteonecrosis has been reported and postulated mechanisms include hyperlipidaemia and fat redistribution associated with antiretroviral therapy
- Rheumatic manifestations such as adhesive capsulitis, Dupuytren’s contracture, tenosynovitis and temporomandibular joint dysfunction have been reported in association with indinavir
- Immune reconstitution inflammatory syndrome

sicca symptoms and may also have extraglandular manifestations. It responds to treatment with antiretroviral therapy with or without steroids.

Effects of antiretroviral therapy

The use of antiretroviral therapy has resulted in a decline in the incidence of DILS and the painful articular syndrome is now uncommon. Reactive arthritis and psoriatic arthritis are also less common.

Many of the above articular syndromes and cutaneous manifestations improve with the use of antiretroviral therapy. As a result some of these patients no longer require NSAIDs or drugs such as chloroquine or salazopyrine.

Some of the rheumatological manifestations which have been reported with the use of antiretroviral therapy are shown in Table III.¹⁻⁵ Many of them are uncommon.

References available at www.cmej.org.za

IN A NUTSHELL

- Arthralgia is common with HIV infection and is usually self-limited or responds to symptomatic treatment.
- Arthritis may develop at any stage of the HIV infection.
- Common manifestations are reactive arthritis, psoriatic arthritis and undifferentiated SpA.
- HIV-associated arthritis may present with polyarthritides, which may sometimes resemble rheumatoid arthritis.
- The risk factors for osteonecrosis (avascular necrosis) include corticosteroid therapy, antiphospholipid antibodies, hyperlipidaemia and HAART.
- Autoantibodies such as antinuclear factor, antineutrophil cytoplasmic antibodies (ANCA), antiphospholipid antibodies and anti-CCP antibodies may occur with HIV infection.
- Rheumatoid arthritis and systemic lupus erythematosus may develop as part of the immune reconstitution inflammatory syndrome (IRIS) in patients on HAART.
- Chloroquine and salazopyrine therapy may be used to treat patients with persistent inflammatory arthritis.
- Immunosuppressive agents such as methotrexate must be used with extreme caution in view of the risk of accelerated viral replication.
- HAART is associated with the amelioration of many of the articular syndromes.

SINGLE SUTURE

Just a little shock to the heart

When the paramedics reach for the defibrillator to treat cardiac arrhythmia, they know the treatment comes at a cost: the powerful bolt of electricity can be painful if the patient is conscious, and may damage the tissues around the heart.

However, the ‘brute force’ approach is considered the only reliable way to combat the disordered pattern of electrical activity in the structurally complicated heart, say Flavio Fenton at Cornell University in Ithaca, New York, Stefan Luther at the Max Planck Institute for Dynamics and Self-Organisation in Göttingen, Germany and their colleagues.

But the team have found that even a mild electric shock – with around 10% of the energy used in standard defibrillation – restores normal heart rhythm to a few isolated areas of a dog’s heart. They also discovered that by carefully timing the delivery of five low-energy pulses these areas expanded to fill the entire heart.

‘Progressively the system goes into a synchronised state and returns to normal rhythm,’ says Fenton.

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