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EVOLVING SPECTRUM OF HIV-ASSOCIATED RHEUMATIC SYNDROMES

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Abstract

At the end of 2013, 35 million people worldwide were infected with HIV. The prognosis of HIV has been transformed by combination anti-retroviral therapy (cART). Providing compliance is good, use of cART has normalised the life expectancy of HIV-infected people leading to a growing population of people with chronic infection. Management of HIV patients has therefore needed to adapt in order to control viral activity but also manage long term complications of HIV and cART. Rheumatological manifestations of HIV were first described in 1989. Since, there have been case reports, case series, and epidemiological studies describing different clinical manifestations of HIV in the musculoskeletal system. This review will encompass musculoskeletal pain, fibromyalgia, systemic lupus erythematosus, and inflammatory arthritis in HIV. We will aim to report on the prevalence of these conditions and the risk factors, explore the impact of the virus on the clinical presentations and discuss implications for diagnosis and management.

Keywords

Pain; Fibromyalgia; Inflammatory arthritis; Systemic Lupus Erythematosus (SLE)

Musculoskeletal Pain and HIV

Pain appears to be common in HIV, with prevalence rates of current pain or ever having experienced pain as high as 60% [1]. Data from time trends seem to suggest that overall cART has not reduced the prevalence of self-reported pain in HIV [1-4]. The following sections will focus on pain reported from the joints (arthralgia) or muscles (myalgia).

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Arthralgia

The results of multiple cohort studies across several continents suggest that pain and stiffness localised to joints (arthralgia) is also common in HIV. Patients define it as one of the most 'bothersome' symptoms of their infection [3]. However, it is difficult draw conclusions as to how common arthralgia is in HIV with prevalence estimates varying widely between 1-79% [3,5-18] and no clear pattern comparing studies carried out pre-cART (1.6%-45%) [5-6] or post-cART [3]. In their large case-control study in San Francisco, Hochberg and colleagues concluded that there was no increase among those with prevalent HIV infection as compared to those without [19]. Notwithstanding the reported variation, the studies suggest that arthralgia is usually intermittent and that arthralgia is most common at the knees, elbows and shoulders [7-8,10]. It is most commonly polyarticular [10] but has been described in just one joint [7].

Painful Articular Syndrome

Berman et al first described this condition in 1988 [9], estimating a prevalence of 10% among US patients in the late stages of the infection. Similar rates were reported subsequently in Argentina by the same author [10]. It was described as different from arthralgia, associated with exquisite pain which is short-lived (lasting between 2-24hours), in the absence of synovitis or other signs of inflammation. Large joints were more commonly involved, though smaller joints (metacarpophalangeal joints) could be affected [10]. The severity of the pain was such that the patients often required admission to hospital for analgesia (commonly with anti-inflammatories or opiates). It is noteworthy that this condition has not been reported in a number of other case series outside of the Americas [7, 14-15,20]. However, 10 cases of painful articular syndrome were described in an Indian cohort study (prevalence 3.3%), where it was associated with distress and sickness absence [16]. Seven of these patients were receiving cART, and three were not. It is therefore unclear whether this manifestation is peculiar to some countries or populations of infected patients. It is possible that it is more common among patients infected with HIV by intravenous drug use but further research is required.

Myalgia

The results of case-control studies suggest that myalgia is almost twice as common among HIV-infected cases than uninfected controls (OR 1.9) [10]. In HIV patients in the pre-cART era, myalgia was reported in 1.7-11% HIV patients [9-11]. Since the advent of cART, prevalence estimates between 0-77% have been reported [3,21]. On the face of it, these raw data might suggest an increase in myalgia since cART, but in a large cohort of female patients there were similar rates among cART-naïve patients as compared with those on stable therapy [22] and in a Thai study, the prevalence of myalgia was reduced after commencement of cART [15]. However, in another study, discontinuation of cART improved the symptoms of myalgia [22]. In some studies, Zidovudine (AZT) use was implicated in causation or exacerbation of myalgia [12]. Therefore it is currently unclear whether treatment improves or exacerbates myalgia.

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Although rates of myalgia have been widely reported in the literature, few studies have incorporated detailed investigation to separate out myopathy or myositis so that the estimated prevalence rates may be misleading.

Fibromyalgia syndrome

The prevalence of the chronic widespread pain syndrome, fibromyalgia has been explored in several studies of HIV patients, particularly in the post-cART era. However, the methodology of these studies has varied widely, particularly in the case definitions utilised. Rates of prevalence between 1-17% have been reported [13-16]. The highest prevalence estimates were in USA [14] and the lower ones in India and China [14,16].

Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune reconstitution inflammatory syndrome (IRIS) describes the phenomenon in which a clinically occult autoimmune inflammatory syndrome is exacerbated or a new syndrome arises de novo after commencement of cART. Many different rheumatic and non-rheumatic conditions have been reported after cART commencement, including sarcoidosis, rheumatoid arthritis, discoid lupus erythematosus, systemic lupus erythematosus, myositis, Grave's disease, Hashimoto's thyroiditis, multiple sclerosis and Adult-onset Still's disease [23]. The mean time to appearance of symptoms after cART commencement is reported as 9 months but symptoms can occur within days of onset of cART.

It has been hypothesised that the mechanism of IRIS relies upon rapid release by cART of memory T-lymphocytes that have been trapped in inflamed lymphatic tissue. More slowly thereafter, there is a slow recovery of naïve T lymphocytes after re-distribution to the periphery and recommencement of thymic production. It should be borne in mind that although cART produces dramatic effects on opportunistic infection and malignancy, and the CD4+ T cell numbers recover, normal immune system function rarely recurs.

Inflammatory arthritis and HIV

There are a plethora of studies describing inflammatory arthritis in the context of HIV infection. However, this is a very heterogeneous literature and standardised rheumatological classification systems have been applied to a variable degree, depending upon availability of rheumatologists and their standard diagnostic tests. For this reason, it is difficult to know to what extent patients described in some studies would be classified differently as for example, 'rheumatoid arthritis 'seronegative arthritis' or 'ankylosing spondylitis' given access to the expertise and relevant tests.

HIV-associated Arthritis

There is currently dispute as to whether there is an 'HIV-associated arthritis'. The first case reports of 'AIDS-associated arthritis' published in 1988, described arthritis developing in patients at an advanced stage of HIV [24]. Hochberg and colleagues disputed its existence after their large San Francisco study [19]. However, since then, other investigators have published data in keeping with this picture, with a prevalence rate ranging from 0.4 – 13.8% [5-7, 9-10,12,13,25]. Most of these studies were from North America, where the estimated

prevalence ranged between 3.8-11%) [9-10,12-13,25]. However, the highest prevalence estimate came from a study in central Africa, where 32 of 39 patients (82%) had an asymmetrical acute nondeforming polyarthritis which was self-limiting [26], making “HIV arthritis” the leading cause of inflammatory articular disease in their cohort. Clearly, it is difficult to differentiate this clinical picture from that of reactive arthritis or even sero-conversion with HIV. The African studies have not reported such high prevalence rates, although most have reported the diagnosis [7,27-28]. Reveille and colleagues described “HIV arthritis” as an acute arthritis of the large joints, lasting less than six weeks, in the absence of either HLA B27 positivity, or radiological changes which was described as distinct from any other recognised rheumatological entity, with no discernible infective triggers, or other classical features in keeping with another recognised inflammatory arthropathy [29].

Assuming its existence as an entity, the literature suggests that the majority of cases have been reported in men, with an average age of 35 years, most commonly in the CDC stage IV of HIV infection (susceptible to ‘other’ disease including AIDS-defining illnesses). The most common presentation was with a relatively mild arthritis, although severe and incapacitating manifestations have also been reported [24]. Self-limitation seems to be universal and it has been reported to respond to symptomatic treatment with either anti-inflammatories or intra-articular corticosteroids [5,24,26-27]. There is minimal evidence of any destructive sequelae or erosive pathology, although it has rarely been followed up long-term. There are a few exceptional cases of synovitis which took a longer time to resolve (up to three months) [8,27-28].

Where laboratory tests were available, this diagnosis was made only in people who were seronegative for Rheumatoid factor, HLA B27 and anti-nuclear antibodies (ANAs). Synovial fluid was inflammatory in nature but with no other diagnostic features. Where data were available, the arthritis was not associated with mucocutaneous manifestations. Synovial biopsy has been rarely carried out but one study found a mild chronic synovitis with mononuclear and plasma cells and no organisms were cultured [24]. Occasional immune complexes were also demonstrated in the synovial fluid in one study [9]. It has been hypothesised that “HIV arthritis” is a type of reactive arthritis, perhaps triggered by the virus.

It is difficult to know what, if any, impact cART might have had on the occurrence of HIV-arthritis, as there are few comparative studies.

Reactive Arthritis

One problem with this literature is that there is apparent overlap of the features of reactive and psoriatic arthritis in some studies [30]. For example, some studies describe patients with PsA who presented with a pustular form of psoriasis indistinguishable from keratoderma blenorrhagica and with features common to reactive arthritis, psoriasis and PsA such as onychodystrophy, conjunctivitis, uveitis, enthesitis, balanitis and dactylitis. It is possible that HIV infection is associated with a new type of psoriatic arthritis which overlaps with reactive arthritis (termed ‘undifferentiated spondyloarthropathy’ by some authors). Of interest, when HLA B27 testing was available, those HIV-infected patients with overlapping

features of psoriatic arthritis and reactive arthritis were often positive for the HLA B27 allele [29] and most HIV-infected patients with PsA who tested negative for HLA B27 apparently did not have these overlapping features [9,12,32]. Unfortunately, few of three available studies have analysed for the HLA allele sub-types typically associated with PsA (Cw6, B17).

Given the classification issues discussed above, it is not surprising that the estimated rate of occurrence of reactive arthritis in HIV pre-cART has varied widely between 0-11%. Interestingly, the higher estimates come from the smaller studies (3.8% [10] - 11% [12]) and the more conservative estimates from larger studies (0.1% [18], 0.2% [33] and 0.5% [19]). Importantly, the largest studies, the San Francisco Men's Health Study (SFMHS), and the Johns Hopkins Multicenter AIDS Cohort Study, recruited > 2000 men who completed a questionnaire, were examined and underwent HIV-antibody testing [19,33] and found no differences in occurrence of reactive arthritis in HIV-infected versus uninfected patients. Similarly, in a study of 1100 unselected HIV patients over 7 years, all examined by one physician, only 1 case of reactive arthritis was diagnosed, as compared with an expected number of 1.4 cases in the local uninfected population and the case occurred prior to HIV acquisition [18].

It is not immediately obvious why the studies in Mexico [6] and Argentina [10] found much higher prevalence rates. It is possible that there is a true difference between North American and Central and South American populations in their susceptibility to reactive arthritis in the context of HIV infection. However, it may reflect more the behaviour underlying mode of acquisition of HIV infection and risk-taking. Reactive arthritis is triggered by a range of organisms but a common group of responsible organisms are those causing sexually transmitted infections (STIs). It seems obvious therefore that people undertaking high-risk behaviours putting them at risk of sexually-acquired HIV are also those at risk of STIs which might trigger reactive arthritis. Certainly, in Spain, where much of the prevalent HIV infection has been acquired though intravenous drug use rather than sexual contact, there appear to be fewer cases [5,11]. In intravenous drug users, the more common musculoskeletal manifestations have been pain and musculoskeletal infections [8,13].

In Black African populations, the HLA B27 allele is virtually unknown and therefore, there was a low prevalence of reactive arthritis prior to the HIV epidemic, even despite a high rate of prevalence of those enteric and urogenital infections that are associated with reactive arthritis. Since 1989, the results of some African studies suggested that the occurrence of reactive arthritis had increased and where diagnosed, it was highly significantly associated with co-existent HIV. For example, out of 65 Zambian patients diagnosed with reactive arthritis, 61 (95%) were HIV-infected [26] and 37.5% of a series of patients in Zimbabwe had reactive arthritis [28]. In other African studies however, there have been lower rates of reactive arthritis, for example in Congo, 7 patients were classified with reactive arthritis over 1-year amongst whom 2 (29%) were HIV-infected. It may be that these discordant data can be explained by case attribution in that, over the same period that the Congo study was carried out, 32 cases of 'HIV arthritis' were diagnosed [35].

The results of Asian studies have also shown no clear picture, as studies from China [14] and Thailand [15] found no cases amongst 98 inpatients and 178 outpatients respectively. In Asia, the principal mode of HIV transmission is thought to be heterosexual, often involving commercial sex workers but, probably because of social stigma, the mode of transmission is frequently undisclosed. The apparent differences in prevalence of reactive arthritis in Asia and Africa may be worthy of further investigation since both continents have a high prevalence of arthritogenic pathogens and, at least as far as is known, HIV infection is transmitted predominantly heterosexually.

Conceivably reactive arthritis might be associated with only the late stages of immunosuppression in HIV. This would explain the apparently low prevalence of reactive arthritis in the US studies where most patients were in the early asymptomatic phase [18-19,33]. Moreover, since cART, there has been less published about reactive arthritis in HIV in the developed world, suggesting perhaps that HIV infection *per se* does not affect the risk. On the other hand though, it could be that high-risk sexual practices have become more restricted since the HIV epidemic, resulting in reduced transmission of arthritogenic urogenital and enteric infections [19]. It is also conceivable that an effective cART regimen could affect the development and course of reactive arthritis. However, a comparison of rates of reactive arthritis among 80 HIV patients, 38 on unspecified single and dual therapy and 42 ARV-naïve appeared to make no impact on the frequency [21]. To confuse the picture further, new reactive arthritis has been reported to emerge on commencement of cART, as a manifestation of immune reconstitution inflammatory syndrome (IRIS) [36]. At present, the epidemiological data pre- and post-cART are confusing and it is impossible to draw clear conclusions about the relationship between HIV infection and reactive arthritis.

Psoriatic arthritis

Skin psoriasis has been reported in association with HIV since the 1980s, with initial reports of psoriasis as a manifestation of end-stage AIDS. In parallel, psoriasiform rash and arthritis has also been described in several cohorts pre- and post-cART [9,12,18,30,32]. The estimated prevalence rates of psoriatic arthritis (PsA) have ranged between 0.02% [20] and 5.7% [12] but most commonly were found between 0.02 and 2%. The estimated population prevalence of psoriatic arthritis is 0.25% in the US, which might imply that HIV increases the risk of PsA. However, the results of the two large US case-control studies [19,33] found no cases of PsA amongst >2000 HIV-infected men but it may be relevant that most of those found infected were in the asymptomatic (early) stage. From a longitudinal study [25], there were 3 incident cases of PsA amongst 395 HIV-infected individuals over 11-years follow-up, (estimated incidence rate 0.07%/annum) which approximates to the 0.05% incidence rate reported in the general population.

In addition to suggesting a possible increase in occurrence rates, the pre-cART studies also reported that HIV-infected patients with psoriasis had more severe and persistent lesions and that the PsA was severe, deforming, erosive and refractory to conventional treatment. However, this again may be influenced by the fact that most cases were in the late stages of HIV (WHO stage 3 and 4) [9,30,32]. The importance of late-stage disease might be best

illustrated by a description of 3 HIV patients with ‘mild’ PsA, amongst whom 1 patient was in the asymptomatic stage, 1 had lymphadenopathy only and only 1 had AIDS [12].

The available evidence from Africa suggested that PsA was uncommon pre-HIV. However, subsequently, a Zimbabwean study involving 64 HIV-infected people with rheumatological symptoms, found 3 patients with severe, persistent PsA, all positive for HLA B17, and one for HLA Cw6 [28]. A Zambian study over 44 months identified 28 patients with PsA amongst 702 (4%) patients with inflammatory arthritis: 27/28 (92%) were HIV-infected, over half of whom were in the asymptomatic stage [37]. In each case, PsA was the first presenting feature of HIV. The skin lesions were extensive and symmetrical occurring simultaneously with a seronegative asymmetrical erosive polyarthritis, typically affecting the lower limbs. Seven of the PsA patients who developed AIDS continued with active psoriatic skin lesions but had a remission of their arthritis in the pre-terminal stages. In Burkina Faso, another study in the post-cART era described only 1 patient with PsA amongst a population of 4084 [20]. Similar rates of prevalence have been found in Asian studies pre- and post-cART [14-15,35].

Soon after the introduction of AZT as the first ART, it was reported that AZT therapy improved skin psoriasis [30]. However, it is less clear what impact cART has on PsA since then. In one Spanish study post-cART, three patients developed psoriatic arthropathy over 7 years of follow-up, none of whom were taking cART [11]. Overall, the epidemiological evidence may suggest that PsA is a feature of end-stage HIV typically in the pre-cART era but the evidence is inconclusive at present.

Ankylosing spondylitis

It is interesting that although Ankylosing spondylitis (AS) is the most common form of seronegative spondyloarthropathy in the Western world, there were very few reports of AS coexisting with HIV infection in the pre-cART era. It has been reported [38], that HIV diagnosed 10-15 years after the onset of AS did not alter its course. More recently however, a small number of cases have been described in France [39], and Burkina Faso [20]. In Africa, as expected given the low prevalence of the HLA B27 allele, cases of AS are rare in the general population and seem to be similarly unusual in HIV. Some authors have suggested that the immunological mechanisms driving AS are independent of CD4+ T cells and therefore are not affected by the infection [38]. However, the diagnosis of AS relies upon features of inflammatory back pain, HLA B27 positivity and radiographic sacro-iliitis. In a study from Zambia, 14 patients presented with spontaneous sacro-iliitis and had positive sacro-iliac stress tests and raised ESR, with normal radiographs [40]. Four of these 14 went on to develop polyarthritis and enthesitis at follow-up and therefore could have been classified with undifferentiated spondyloarthropathies. Longer term follow-up would be needed to determine whether these patients developed diagnostic features of AS. In most cohort studies referenced in this review, undifferentiated spondyloarthropathy appears to be common and it may be that a proportion of AS is being classified as undifferentiated spondyloarthropathy in the absence of radiographic studies or HLA B27 testing or long enough duration of follow-up.

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Rheumatoid arthritis

The earliest mention of rheumatoid arthritis (RA) and HIV came from case reports pre-cART describing patients with established RA who experienced clinical improvement or remission after the development of HIV [41]. This clinical phenomenon could be explained if the HIV-associated depletion of CD4+ helper/induced lymphocytes was reducing the immunogenic autoimmune activity which maintains activity of RA and this led to an early view therefore that HIV and RA were mutually exclusive diagnoses.

However, around the same time Berman and colleagues described an HIV-infected patient with an RA-like symmetrical polyarthritis who was Rheumatoid Factor (RF) negative [9]. The patient had radiographic erosive changes and their symptoms lasted longer than 6 months, clearly differentiating it from other types of presentation such as painful articular syndrome and reactive arthritis. Given the conviction that arose that RA and HIV were mutually exclusive, the cases subsequently described took different approaches in describing inflammatory arthritis in HIV. Some researchers described patients with a symmetrical erosive arthropathy as having RA whilst others have described it as one end of a spectrum of inflammatory arthritis seen in HIV, with this pattern generally more destructive and symmetrical than the others. Rosenberg et al in 1989 discussed the radiological features of four patients as being ‘rheumatoid-like’ [42] but labelled the condition ‘acute symmetrical polyarthritis’, likely because it was thought the two conditions were mutually exclusive [43].

Whatever the nomenclature, there is a steadily growing body of global evidence that HIV-infected patients in the post cART era can develop a new symmetric polyarthritis involving the small joints of the hands and feet, clinically suggestive of RA [9,14,16-17,39]. For example, one Zimbabwean study described 8/64 patients with arthritis and prevalent HIV infection who had a symmetrical polyarthritis affecting the hand and wrist joints, 3 of whom were positive for rheumatoid factor and one of whom developed radiographic erosions [28]. The authors postulated that some of these 8 patients had true rheumatoid arthritis and that others had a ‘symmetrical rheumatoid-like arthritis occurring with HIV’. Across the range of studies, estimated rates of prevalence range between 0.1-5% [13,16-17,20,28,36,39]. It seems that most cases developed at a minimally advanced stage of HIV disease, i.e. with CD4+ counts >200 cells/mm3, and/or when there was an undetectable viral load [16,39,44]. Rheumatoid arthritis arising as an immune reconstitution syndrome has also been described [36,45].

A predominance of the cases of RA has been reported among men but this almost certainly reflects the much larger numbers of HIV-infected men available for epidemiological studies. Certainly, Stein et al found an equal gender distribution amongst their population, despite their relatively male population [28]. The reported average age at diagnosis ranged between 27-58 years [28] with a range of duration of cART between 8 months and 9 years [44-45]. In one study, smoking was a common risk factor with 50% of those developing RA being cigarette smokers.

Since rheumatoid factor is not a specific autoantibody, it is unsurprising that very high rates of occurrence of sero-positivity to rheumatoid factor (35-47%) were reported in early HIV studies pre-cART [5,46]. Since ART, it appears that the background prevalence of

rheumatoid factor has dropped [6] with rates comparable to those found in general population studies after treatment with cART [16,28]. Anti-cyclic citrullinated peptide (ACPA) antibodies have rarely been assayed in HIV studies. There is evidence of increased rates of ACPA as high as 15% in HIV patients not taking cART but that these rates drop to <6% after 6 months of treatment with cART [46].

As far as clinical features are concerned, rheumatoid nodules have been described in HIV patients [45] although not necessarily associated with sero-positivity for rheumatoid factor. Radiographic erosions have been seen in these patients [13,28,42-43], as has peri-articular osteoporosis.

Connective tissue diseases

Systemic Lupus Erythematosus

The first available case report describing co-existent HIV and Systemic Lupus Erythematosus (SLE) was published in 1988 [47]. Since, our review found more than 100 cases in the literature but considering publication bias, it seems likely that this coexistence is uncommon. The association between HIV infection and this and other autoimmune diseases is becoming increasingly recognised, and in particular, the immunological environment seen in HIV could provide an important insight into the intriguing pathogenesis of the two diseases.

When the two conditions coexist, interesting diagnostic as well as therapeutic dilemmas are raised. The two conditions have many similarities; both are systemic diseases which can present with vague, non-specific symptoms in a wide range of different ways. Secondly, HIV infection disrupts the immunological milieu, giving rise to auto-antibodies, which may play an aetiological role in auto-immune disease. In addition, the pathogenesis of both conditions relies upon a crucial role of CD4+-lymphocytes.

Clinical features—HIV and SLE have overlapping features of dermatological, renal, neurological, arthritic, and haematological abnormalities, as well as constitutional symptoms such as fever or weight loss. Presentation with lymphopenia, haemolytic anaemia and/or thrombocytopenia is common with both conditions. Neurological features of both may include psychosis, peripheral neuropathy and focal deficits. Renal disease is another common manifestation of both diseases, especially in those who acquired their HIV infection by vertical transmission (mother-to-child) [39,48].

Epidemiology—Of the cases in the literature which discuss the coexistence of these two conditions, 88 were identified in the cART era. In their review, Barthel and Wallace estimated that there would be around 400 co-existent cases by 1993, given that approximately 500,000 Americans have SLE, and 200,000 were expected to have AIDS, providing that the conditions were not mutually exclusive [49]. Given the limited numbers reported to date, it is possible that the opposite is true. Certainly, even amongst the largest, best-characterised cohorts of HIV patients, few cases of SLE have been described either diagnosed prior to infection or arising de novo. At a South African centre, between 2003-12 Mody et al diagnosed 13 people with co-existent disease [50]. Among 52 HIV-infected

patients presenting with any autoimmune disease in France, only 5 fulfilled diagnostic criteria for SLE [39]. It is however possible that SLE is under-diagnosed, and the symptoms misattributed to the infection. Moreover, because there can be a very long latent period between HIV seroconversion and clinical presentation, it may be that co-existent disease is misattributed as SLE or retrospectively attributed to the HIV post-diagnosis. [47,51-55].

In keeping with the well-known epidemiology of SLE, the average age of patients described with co-existent diagnoses is around 30 years, with approximately 70% of the cases occurring in women. Those individuals with pre-existing HIV infection who then went on to develop SLE were slightly older (mean age 33 years) although the true average age at onset is likely to be older since children who acquired the infection through vertical transmission were omitted from the analysis. The average duration between HIV-infection and SLE onset was 8.9 years. It has been argued that people with HIV develop later onset SLE, either because of the role played by retroviruses in instigating auto-immunity, or conversely because the presence of HIV delays the onset of the condition but it is also possible that the symptoms of developing SLE are wrongly attributed to the HIV, leading to later diagnosis.

In the following section, those case reports from the literature with sufficient detail are described, subdivided chronologically depending on timing of disease presentation or diagnosis (not all of the case reports included a time-line, and therefore have not been included).

i) Pre-existing SLE, with acquired HIV infection: Twenty seven cases were identified of individuals with established SLE, who subsequently acquired HIV infection. Of these, the majority had experienced a clear improvement in their disease activity after infection; with many going into partial, if not total, remission [39,50,56-65]. These results implied that, as with RA, active HIV infection was protective against SLE activity. Additionally, after commencement of cART, two patients remained stable [17,50], whilst one experienced a significant flare of SLE six months after cART (CD4 count 102 cells/mm^3) manifest with a rash and transverse myelitis [58].

ii) Cases of known HIV infection, who develop SLE – or 'Lupus-like' manifestations: Thirty eight cases have been reported to date of individuals known to have HIV infection, who developed SLE or similar symptoms [50,66-67]. Many of the authors however have coined the phrase 'lupus-like' presentation, given that they do not always fulfil the American College of Rheumatology (ACR) criteria for SLE, which specify the absence of a significant other condition which could cause a similar clinical picture. Of note, there was a paucity of data in some case reports.

Among those reports in which the SLE was defined as fulfilling the ACR diagnostic criteria, the new pathology ensued on a background of previously controlled HIV infection so that changes in clinical markers of HIV indicated that there was a second de novo disease process (for example, CD4+ count >200, or low viral loads) [50,66-67]. Seventeen of these patients were receiving cART. One report described a case of de novo SLE among a family in which there were six cases of familial SLE, one member (who acquired HIV) developed autoimmunity following the initiation of cART, suggesting a genetic predisposition with an

environmental trigger [68]. Where auto-antibody levels were available, about half of cases were dsDNA positive, and dsDNA positivity was associated with high titres of ANA. Some case reports described hypocomplementaemia when SLE activity was the predominant feature [58,67]. In HIV infection without SLE, it is common to have low titres of ANA, but rarely are they high, or are dsDNA auto-antibodies found [6,47].

Lupus nephritis was diagnosed in three people with pre-existing HIV disease in association with systemic features of SLE [48,69-70]. It is noteworthy that so-called 'lupus-like' glomerulonephritis is a recognised finding in HIV-positive individuals, among patients who do not necessarily develop any other clinical or immunological feature of SLE [71].

ii) Concurrent diagnosis of HIV and SLE: Given the long duration between sero-conversion and diagnosis with HIV in some patients, it is difficult to be certain of the precise timing of onset of either condition in some of the published reports. We found 12 cases in the literature in which patients were diagnosed with both conditions on the same admission. The majority of these cases met the ACR criteria for SLE (although many of the criteria overlap in the two conditions). The average CD4+ count on presentation was 448.5 cells/mm3 (range 271 – 660 cells/mm^3).

iii) Immune restoration SLE: As described earlier, several patients have been reported to develop immune reconstitution SLE after commencement of cART. In those patients reported, the average CD4+ count before the flare of SLE was 397cells/mm3 (range 76 – 574 cells/mm3). Immune reconstitution was reported as soon as 2 months after the initiation of cART but also more than 5 years after commencement [68]. In the latter case, it is more difficult to be certain that the SLE is really developing as a consequence of 'immune restoration'. Follow-up of these patients suggested that both conditions remained stable on cART [50,66-67].

Pathogenesis of SLE in HIV—The presence of auto-antibodies is a common finding in patients with HIV, with reported prevalence rates of anti-nuclear antibodies (ANAs)being up to 17-23% of patients, but most of whom were on early HIV therapy in the form of monotherapy with AZT (with the average CD4+ count <400 cells/mm3)[6,47]. These rates are slightly higher than those found in the general population. In these HIV studies, the ANAs were usually of low titre, and of a non-specific speckled pattern and double-stranded DNA antibodies were rarely associated. It is unclear if such high rates of ANAs are seen among HIV patients treated with cART according to modern best practice guidance. Either way, ANAs of low titre are rarely pathogenic and their presence does not signify a raised risk of development of SLE. Double-stranded DNA antibodies are usually not found in isolated HIV infection and where present, they are of low avidity. In some cases of people with prevalent SLE with double stranded DNA antibodies, these antibodies became undetectable after acquisition of HIV infection [47,60,63,72].

In conclusion, the co-existence of HIV and SLE is rare, but noteworthy, and likely to reflect an almost mutually exclusive relationship. Whilst advancing HIV disease can lead to suppression of auto-immunity, the reverse can also be true. Clinicians need to remember the importance of testing for HIV, especially in atypical cases or those resistant to treatment.

Anti-Phospholipid syndrome (APS)

As with other auto-antibodies, anti-cardiolipin antibodies (aCL) were shown to be common in patients infected with uncontrolled HIV. In a pre-cART study, aCL IgG was found in 94% of HIV patients (n=74) compared to no controls [6]. This is similar to findings from other studies [9,73], but higher than other cohorts where the prevalence was 13-64% (74-77). The prevalence was higher among those with advanced HIV disease (73). Similarly lupus anticoagulant was found in 3-46% of patients in advanced stages of HIV not receiving cART (78-79), and was associated with the AIDS-defining illness *Pneumocystis Jirovecii* (80). Much lower rates of prevalence have been shown in patients taking cART, including a Nigerian study, which found a prevalence of LA antibodies of 5%.

The risk of venous thrombo-embolism (VTE) has been shown to be elevated in individuals infected with HIV, though there is little evidence that the presence of APS auto-antibodies are contributory [73,76-77]. HIV patients are at risk of many complications associated with increased VTE, including obesity, immobility, cardiovascular disease, and cigarette smoking, Intravenous drug use is another independent risk factor. There have been a few isolated reports of VTE in individuals with HIV and anti-phospholipid antibodies [81-82], although given the many other potentially contributory factors in these individuals, and the rarity of this finding, it is difficult to postulate a major risk of clinical anti-phospholipid antibody syndrome in HIV at this time.

Diffuse Infiltrative Lymphocytosis Syndrome (DILS)

Diffuse infiltrative lymphocytosis syndrome (DILS) is a Sjögrens-like multi-system condition seen in HIV-infected individuals. It typically causes salivary gland swelling and chronic sicca symptoms. The commonest presentation is with bilateral parotid gland enlargement, seen in 88-100% of presentations [83-84] but there can be isolated sicca symptoms, without gland enlargement. Extra-glandular manifestations similar to those of Sjogren's have also been described, including lymphocytic infiltrative pneumonitis (31-59%), myositis (26%), hepatitis (4-23%), neuropathology (24%), nephropathy, neuropathy (23.5%), and other lymphoid tissue infiltration causing hepatomegaly, splenomegaly, and generalised lymphadenopathy [83-85]. Pseudo-tumours have also been seen in non-lymphoid tissue such as the skin, CNS, and digestive tract [85]. Panuveitis has also been reported [86]. Neurological features are also described including sensory neuropathy, mononeuritis multiplex, radiculopathy, facial nerve palsy, and lymphocytic meningitis [87]. Neoplastic conversion to Non-Hodgkin's lymphoma from DILS has been described, with three patients in the Houston cohort [83], two soon after presentation with DILS, and the third six years later.

To make the diagnosis [88], there needs to be histological confirmation of salivary or lacrimal lymphocytic infiltration, with granulomatous or neoplastic aetiologies excluded. DILS differs from Sjögrens in that patients tend to be anti-Ro/SSA and anti-La/SSB negative, with CD8+ rather than CD4+ glandular tissue infiltration; indeed the presence of elevated titres of circulating and infiltrating CD8+ lymphocytes is a key feature in the pathophysiology of this disorder.

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Pre-cART, DILS was a very common clinical manifestation associated with HIV infection. It appears to be have been particularly common in the Afro-American, and Black African communities such that 60% of an American cohort were Afro-American [84] and a prevalence rate as high as 48% was reported in a West African population pre-cART [89]. One group reported a prevalence of 33.7% among people with HIV referred to their Rheumatology service between 1994 and 1997, and that the rate dropped to 7.5% over the six years after widespread availability of cART [83]. However, there are cases of DILS in whom the CD4+ count was not markedly reduced [87]. Treatment with cART seemed to improve the symptoms in the majority, with adjunctive glucocorticoids required in a minority. Of note, there has been limited epidemiological data since cART to inform as to whether the condition has been eliminated.

Treatment of Inflammatory rheumatic disease in the context of HIV

There is a significant challenge in treating inflammatory rheumatic disease in the context of HIV. Certainly, use of rheumatological therapies in the pre-cART era suggested that they may have a deleterious effect on patient health and in some cases, precipitate death [30, 32]. However, among patients taking cART reliably and with complete suppression of viral activity, use of standard rheumatological therapies appears safe and well-tolerated, particularly if the CD4+ count is above 200 count/cells/mm^3.

Glucocorticoids

Glucocorticoids have been widely used in HIV-infected patients for the treatment of a range of inflammatory conditions. The same toxicities occur in HIV patients as those described in the general population. Moreover, the commonly used protease inhibitor ritonavir inhibits steroid metabolism through cytochrome P450 inhibition [90]. This leads to enhanced glucocorticoid activity by up to 50%, so that doses should be adjusted accordingly. Importantly, patients with HIV are at increased risk of low bone mass, osteoporosis, fractures and avascular necrosis so that appropriate bone protection should be considered in all patients, particularly those taking ritonavir.

Anti-malarial therapies

It has been shown that Hydroxycholoroquine (HCQ) inhibits HIV infectivity through immunomodulatory effects, inhibit viral replication and increase circulating CD4+ T cells [91-93]. Therefore, hydroxychloroquine can be used safely, with possible HIV benefits, as first-line therapy for rheumatoid arthritis, DLE or SLE.

Sulfasalazine

The use of Sulfasalazine in HIV-infected patients has steadily increased. From three published reports including 17 patients with HIV and seronegative spondyloarthropathy, there is evidence of a good response in the majority of patients (14/17= 82%) (often in < 1 month) and no bone marrow, renal or liver toxicity [94].

Methotrexate

In the case of methotrexate, most reports in the pre-cART era reported poor outcomes, and even death [30]. Since however, there have been increasing numbers of case reports of its safe, effective use among patients with psoriasis, psoriatic arthritis, RA and dermatomyositis over the course of months and even years. It may be that methotrexate does not adversely affect the natural course of HIV disease but instead reflects publication bias. The use of methotrexate is now recommended for the treatment of refractory severe psoriasis by the National Psoriasis Foundation in their 2009 guidance (grade III evidence) [95].

Leflunomide

There are limited data on the use of Leflunomide for HIV-infected patients with inflammatory rheumatic syndromes. However, leflunomide has been shown to have virostatic properties against several viruses, including HIV-1, so that it may be a safe drug to use in the context of HIV [96]. HIV patients have increased predisposition to hepatotoxicity and therefore liver function would require close monitoring in patients receiving Leflunomide.

Azathioprine

There were few data on the safety of azathioprine in HIV but a recent review of its use in 7 patients suggested that it had been used safely, without opportunistic infections, over a median of 12 months although two died but the authors stated ‘either death was associated with azathioprine therapy’ [97]. Of note, the only rheumatic syndrome treated with azathioprine in this series was myositis in one patient. More data are required.

Cyclosporin-A

Cyclosporin-A has been used in HIV patients, particularly in the context of organ transplantation, those with nephritis and dermatological patients. There are complex drug interactions between Cyclosporin-A and protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Long-term careful monitoring would be required.

Mycophenolate Mofetil

There are few data on the use of Mycophenolate (MMF), except in renal and SLE patients [39,98-99]. There have been in vitro and in vivo studies showing that MMF has some promising anti-viral activity against HIV-1.

Anti-TNF alpha therapies

There have beenincreasing numbers of case reports of use of anti TNFα therapies in HIV, including: Infliximab, Etanercept and Adalimumab. They have been successfully used in psoriatic arthropathy, AS, RA, Crohn’s, Spondyloarthropathy and Reiter’s syndrome [100-103]. Generally, the cases in the literature record an excellent response, often occurring rapidly, although it is important to bear in mind that there may be significant reporting bias. In the largest published series, 6/8 responded well but the longest duration of follow-up was under 3 years and 1/8 experienced a serious infection. In one case report, the patient experienced frequent secondary infections which required discontinuation after 4 months

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(CD4<50). There are few long term data published presently but one patient, co-infected with HIV and Hepatitis C was successfully treated with infliximab over 11 years of follow-up without serious infection [103]. When considering initiation of anti-TNF therapies, serious consideration should be given to screening for TB and one should have a low threshold for involving a respiratory physicians and prophylactic administration of anti-TB chemotherapy.

Conclusion

The profile of musculoskeletal manifestations of HIV infection has gradually altered since the advent of cART. Arthralgia and myalgia are very common manifestations pre- and post-cART. Rheumatoid arthritis and SLE, previously thought to go into remission in active HIV infection, seem to develop de novo or be reactivated by effective cART. Seronegative arthropathy, with and without axial involvement, are observed globally although it is difficult to obtain accurate data as to prevalence due to differences in classification. With appropriate careful monitoring and pre-treatment screening, there is growing evidence that inflammatory autoimmune rheumatic diseases can be treated with conventional anti-rheumatic therapies, although there are no randomised controlled trials in HIV patients and few data as to long-term safety.

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Practice Points

- Musculoskeletal symptoms are common in HIV and life expectancy has normalised so that it is likely that more people with HIV will be referred to rheumatologists
- Most of the autoimmune inflammatory rheumatic diseases have been described in HIV patients
- There is potential for drug interaction with anti-retroviral therapies and care should be taken before initiating any prescription
- In stable HIV, well-controlled on cART with undetectable viral load and CD4+ count above 200 cells/mm^3, most of the disease modifying anti-rheumatic drugs can probably be used but there are few published data and careful monitoring is mandatory

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Research agenda

- Some high-quality case-control studies among HIV infected cases and appropriate control populations are still needed to determine if HIV increases the risk of rheumatic syndromes, particularly seronegative disorders
- More data are urgently needed on the safety and efficacy of use of biologic therapies and disease modifying drugs in HIV patients