The changing spectrum of rheumatic disease in HIV infection

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Background: Rheumatic manifestations were described soon after human immunodeficiency virus (HIV) was discovered. Since however, combination anti-retroviral therapy (cART) has revolutionized the course of the infection. Less clear is what effect cART has had on rheumatic manifestations.

Sources of data: References were retrieved from the PubMed database using keywords including: ‘HIV’ and ‘arthritis’; ‘myalgia’; ‘arthralgia’ and other disease-specific terms, e.g. ‘rheumatoid arthritis’.

Areas of agreement: Musculoskeletal pain was common in HIV and increased with AIDS. Immune restoration inflammatory syndrome on initiation of cART causes de novo autoimmune inflammatory rheumatic disorders. Seronegative inflammatory arthritis with/without axial involvement has been reported widely with HIV.

Areas of controversy: It is unclear if HIV causes these conditions, creates an environmental milieu supportive of these conditions or acts as a marker of other risk factors. It is unclear what effect cART has had on these conditions.

Growing points: Variable diagnostic classification criteria have caused this literature to be poorly comparable.

Areas timely for developing research: High-quality controlled epidemiological studies using standardized criteria are needed among cART users. Treatment of active autoimmune disease in HIV patients needs to be evaluated formally.

Keywords: HIV/rheumatic manifestations/immune reconstitution inflammatory syndrome (IRIS)/combination anti-retroviral therapy (cART)

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Introduction

The earliest report that the human immunodeficiency virus (HIV) might be associated with rheumatic manifestations was 3 years after the discovery of the virus when Winchester et al.1 described 13 patients
affected by painful, disabling asymmetrical inflammatory arthropathy in end-stage HIV/AIDS. This initial publication sparked a number of studies with some, but not all, suggesting an excess risk of seronegative inflammatory rheumatic disorders. Since then, at least in the developed world, anti-retroviral therapies, particularly in combination (cART) have changed the course and prognosis of HIV infection. This review will contrast the evidence published pre-cART and in countries where cART is not widely available with studies published since cART.

**Arthralgia and myalgia in HIV**

Myalgia and arthralgia are common in primary HIV seroconversion illness. Before cART, severe, disabling pain was common in HIV/AIDS. For example, 60% of 438 ambulatory AIDS patients reported pain averaging 5.4/10 in intensity.² Prospectively over 2 years, 95 AIDS patients reported incident pain.³ Most (60–70%) of those with pain experienced significant functional effects²,⁴ and had measurably poorer quality of life.⁵ Many early studies did not dissociate musculoskeletal pain from pain of other origins, e.g. neuropathic. However, where differentiated, much of the burden appears to be musculoskeletal with arthralgia and back pain two of the most common sites.⁶ Pain in the legs (43%), back (31%) and arms/hands (26%) were the three of the four most common sites of pain in 148 ambulatory HIV patients.⁴

**Myalgia**

In the pre-cART HIV literature, the distinction between myalgia and myositis is frequently unclear, either because investigations were not carried out⁷,⁸ or because different diagnostic methodologies were used [creatine phosphokinase (CPK), EMG, biopsy]. In a large case series,⁹ 9 out of 10 cases of myalgia had high CPK, but only one of eight biopsies showed myositis. With the classification variability, it is unsurprising that diverse prevalence rates are estimated (Table 1).

Since cART, there is evidence that myalgia remains common, affecting 77% of 109 HIV-infected patients in one study.¹⁰ In comparison with all other possible symptoms, patients rated muscle pain the third most bothersome and the majority (74%) attributed it to HIV or cART (30% to HIV; 22% to cART and 22% to both).¹¹ A study of HIV-infected women and non-infected controls found that myalgia (muscle aches/pains) was considerably more common among cases [odds ratio (OR) 1.9].¹² However, different rates of prevalence were also found between women stable on cART and those who had
Table 1 Prevalence of arthralgia and myalgia in HIV.

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence of arthralgia among HIV group (%)</th>
<th>Prevalence of myalgia among HIV group (%)</th>
<th>Prevalence in HIV-negative controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-cART</td>
<td></td>
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<tr>
<td>Calabrese et al.(^7)</td>
<td>8 cases (7%) Myalgia/ myositis</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>Muñoz Fernández et al.(^17)</td>
<td>9 cases (1.6%)</td>
<td>25 cases (4.5%)</td>
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<td>—</td>
</tr>
<tr>
<td>Monteaqudo et al.(^32)</td>
<td>12% (13) arthralgia and/or myalgia</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>Berman et al.(^16): 101 cases; 92% male</td>
<td>35 cases (35%)</td>
<td>10 cases (10%)</td>
<td>2 cases (2%) arthralgia</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Berman et al.(^16): 89 HIV cases, 80 controls; 85% male</td>
<td>23 cases (26%)</td>
<td>10 cases (11%)</td>
<td>0 cases myalgia</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Casado et al.(^25)</td>
<td>2 cases (2.7%)</td>
<td>1 case (1.7%)</td>
<td>—</td>
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</tr>
<tr>
<td>Post-cART</td>
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<td></td>
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<tr>
<td>Simms et al.(^8): 81% of rheumatology patients taking AZT</td>
<td>37 cases (26%)</td>
<td>16 cases (12%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Medina-Rodriguez et al.(^13): 74 HIV cases, 72 controls; 86% male</td>
<td>34 cases (45%)</td>
<td>23 cases (31%)</td>
<td>2 cases 2% arthralgia</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Richman(^58): placebo-controlled RCT of AZT in HIV</td>
<td>8% of those receiving AZT when compared with 2% receiving placebo</td>
<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>Solinger and Hess(^14)</td>
<td>8 cases (0.7%)</td>
<td>7 cases (0.6%) (AZT)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Buskila et al.(^15): 52 HIV-infected patients on zidovudine</td>
<td>21 cases (40%)</td>
<td>18 cases (35%) (AZT)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Berman et al.(^37): (47% mono/dual ARVs)</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Marquez et al.(^21): (100% cART)</td>
<td>35 cases (47%)</td>
<td>10 cases (13%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Calabrese et al.(^11): (32% cART)</td>
<td>8 cases (2%) non-inflammatory myositis</td>
<td>2 cases (0.5%) inflammatory myositis</td>
<td>0.5% non-inflammatory myositis (2)</td>
<td>—</td>
</tr>
<tr>
<td>Duran et al.(^59): 336 HIV-infected patients starting cART</td>
<td>Muscular pain: 32.7%</td>
<td>1 month and 32.1% 4 months after starting cART</td>
<td>‘Distressing’ muscular pain: 12.8% at 1 month and 10.4% at 4 months</td>
<td>—</td>
</tr>
</tbody>
</table>

Continued
discontinued cART with higher rates (32.3 vs. 26%) among those who had discontinued\textsuperscript{12} (Table 1).

One anti-retroviral, zidovudine (AZT) has been particularly implicated in myopathy from multiple epidemiological studies in the early 1990s, when it was the foremost anti-retroviral.\textsuperscript{8,13–15} Interestingly, when patients on AZT had a muscle biopsy, some, but not all, showed evidence of inflammatory change and cessation of the AZT did not always successfully treat the pain.\textsuperscript{9}

\textbf{Arthralgia}

Widely different rates of prevalence have been published for arthralgia, i.e. pain localized to joints. These range from 0.7\textsuperscript{14} to 45\%\textsuperscript{13} (Table 1), but the studies are very heterogeneous including, for example, different methods of assessment of the outcome (some studies have measured the prevalence of myalgia with arthralgia), and different populations (proportion of men; ethnicities; modes of acquisition; duration and stage of infection). Few studies are case-controlled, but two small controlled studies found significantly more arthralgia among cases.\textsuperscript{13,16} Despite the study variability, there is surprising concordance

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
 & Prevalence of arthralgia among HIV group (\%) & Prevalence of myalgia among HIV group (\%) & Prevalence in HIV-negative controls & $P$-value \\
\hline
Johnson et al.\textsuperscript{10}: 109 HIV infected patients on cART; 88\% male & Stiff, painful joints: 78.9\% (second most bothersome symptom) & Aching muscles: 77.1\% (third most bothersome symptom) & & \\
\hline
Silverberg \textit{et al.}\textsuperscript{12}: 1256 HIV infected women; 364 HIV-negative controls & – & 26.7\% cART naive 26\% cART stable 29.7\% cART regimen change 32.3\% cART discontinuation of all drugs & 16.5\% & OR 1.9 for cases compared with controls ($P<0.05$) \\
\hline
Silverberg\textsuperscript{60}: 1574 HIV infected women (WIH); 955 HIV infected men (MAC) & – & Women: age <40 years: 20.3\%; age 40–50 years: 29.9\%; age >50 years: 34.2\%  
Men: age <40 years: 14.2\%; age 40–50 years: 16.2\%; age >50 years: 20.6\% & & \\
\hline
\end{tabular}
\caption{Continued}
\end{table}
about the clinical features of arthralgia in HIV, described as mild, intermittent and polyarticular, affecting predominantly knees and shoulders and to a lesser extent, the metacarpophalangeal joints and elbows.\textsuperscript{8,13–18} In two US epidemiological studies, both including controls, neither cases nor HIV-negative controls were found to have myalgia or arthralgia and the principal explanation for this was thought to be that most of the study subjects were in the asymptomatic stages of HIV infection.\textsuperscript{19,20}

Since the advent of cART, early clinical trials rarely included arthralgia as an outcome, but more recent data suggest that it remains common. For example, 79\% of 109 HIV-infected adults on cART reported stiff, painful joints during the past 1 month\textsuperscript{10} and after fatigue, this was the second ‘most bothersome’ symptom which most attributed to HIV or cART (33\% to HIV; 14\% to cART and 18\% to both).

**Soft tissue rheumatic complaints**

Despite their ubiquity in the general population, there has been little research into the frequency and impact of such complaints in HIV. In those studies available, the absence of controls and prospective data limits the interpretation of results.\textsuperscript{19,20}

*Carpal tunnel syndrome*

Studies pre- and post-cART have suggested that carpal tunnel syndrome may be more common in HIV-infected patients and may occur at a younger age.\textsuperscript{9,17,21–23} A role for protease inhibitors (PIs) in causation has been hypothesized, perhaps through metabolic adverse effects,\textsuperscript{23} but cases of carpal tunnel syndrome occurring among two women on PIs without evidence of metabolic anomalies such as weight gain and lipodystrophy have been documented.\textsuperscript{24} Clearly, more research is required in this field.

*Tendonitis*

In one case–control study, a significantly greater risk of tendonitis was reported among 74 HIV-infected cases (22/74 = 30\%), when compared with 72 uninfected controls (\(P < 0.001\)).\textsuperscript{13} Tendonitis has also been reported in other case series.\textsuperscript{9,25,26} Once again, more research is indicated.
Shoulder capsulitis

Shoulder capsulitis has been reported in several case series.\textsuperscript{9,27,28} PI exposure, in particular to indinavir, has been implicated.\textsuperscript{27,28} Indinavir has also been associated with Dupuytren’s contracture, temporo-mandibular dysfunction and de Quervain’s tenosynovitis.\textsuperscript{27}

Fibromyalgia syndrome

The prevalence of fibromyalgia syndrome has been investigated in several HIV cohorts, mostly post-cART.\textsuperscript{8,9,13,21,29,30} These studies have varied in terms of methodology, sampling frame and diagnostic criteria and therefore have produced different results. Ranging from 1%\textsuperscript{30} in a cross-sectional study in China using the ACR case definition, 7–12% in studies in Thailand,\textsuperscript{29} USA\textsuperscript{8} and Mexico,\textsuperscript{13} 17% in another US study\textsuperscript{21} through to 29% in a Canadian study,\textsuperscript{15} using the Smythe case definition, the ‘true’ prevalence is likely to lie within this range, but more research is required. In one study, risk factors for fibromyalgia were: longer mean duration of HIV \((P=0.01)\), female gender \((P=0.03)\) and a history of depression \((P=0.001)\) compared with HIV patients without fibromyalgia,\textsuperscript{8} but another study found no significant difference in gender, mode of transmission, stage of infection or cART between HIV-infected patients with and without fibromyalgia.\textsuperscript{29} A comparison of fibromyalgia occurring in HIV patients when compared with the general population suggested that HIV fibromyalgia occurred more often in men \((P=0.001)\) caused shorter duration of rheumatic symptoms and was more likely to be associated with depression, but otherwise was clinically indistinguishable from ‘normal’ fibromyalgia.\textsuperscript{13} A recent review of the relationship between fibromyalgia and infection postulated that HIV might disrupt the hypothalamic–pituitary–adrenal axis, cause sleep disturbance and depression which might all contribute to fibromyalgia.\textsuperscript{31}

Painful articular syndrome

Twenty-three cases of ‘painful articular syndrome’ were found in the literature. First described by Berman et al.\textsuperscript{16} as ‘severe, sharp articular pain of short duration (2 to 24 h) requiring anti-inflammatory and/or non-narcotic or narcotic drugs’, they reported a prevalence of 10% among 101 HIV-positive patients in the late stages of infection. This disorder is apparently distinguishable from the arthralgia discussed above as the pain is excruciating and debilitating leading to hospital treatment in
more than half of patients. None of the patients had synovitis or other physical findings of inflammation. The joints most commonly involved were the knees, shoulders and elbows.16 Two case–control studies found a prevalence of 6 and 8% respectively, compared with no cases in HIV-negative controls.13,18 Most of these patients were in the late stages of HIV infection. Since, a study in Thailand reported two cases presenting to a rheumatology clinic over a period of 6 years29 both of whom responded to indomethacin and a study of 98 Chinese inpatients reported one case.30 We found no reported cases of this syndrome from Africa to date, and the effect of cART on this syndrome is currently unclear.

Inflammatory arthritis and HIV

Reactive arthritis

The estimated occurrence of reactive arthritis in HIV pre-cART varies between 0 and 11% (Table 2). However, the higher estimates come from the smaller studies (3.815–11%18), with more conservative estimates from larger studies (0.114, 0.220 and 0.5%19). The larger US 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.19,20 Comparison of the rates of incidence or prevalence of reactive arthritis in HIV-infected vs. uninfected patients found no differences. Solinger and Hess14 prospectively studied 1100 unselected HIV patients over 7 years, all examined by one physician. Having estimated the prevalence of reactive arthritis in the local uninfected population, the expected number of cases for the HIV-infected cohort was 1.4. In fact, only one case of reactive arthritis was observed, diagnosed prior to HIV acquisition.14

It is difficult to explain why the studies in Mexico13 and Argentina18 found such different results. It may suggest a true difference between North American and Central and South American populations in terms of susceptibility to reactive arthritis in the context of HIV infection. However, it may reflect more the behaviour underlying risk taking and mode of acquisition of HIV infection than a risk of reactive arthritis associated with prevalent HIV infection. Reactive arthritis may be triggered by many different organisms, but one of the most prominent groups of triggering organisms is those causing sexually transmitted infections (STIs). It may be that those at risk of sexually acquired HIV are those at risk of STIs which might trigger reactive arthritis. Certainly, in Spain, where much of the prevalent HIV infection has been acquired through intravenous drug use rather than sexual contact, there appear to
### Table 2 Reactive arthritis in HIV-infected populations.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of study subjects</th>
<th>Study design</th>
<th>Proportion of population infected with HIV</th>
<th>Cases of reactive arthritis</th>
<th>Cases of psoriatic arthritis</th>
<th>HLA B27</th>
<th>HLA Cw6</th>
<th>HLA B17</th>
<th>Diagnosis by a rheumatologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simms et al.</td>
<td>140</td>
<td>Cross-sectional</td>
<td>100%</td>
<td>0</td>
<td>12 cases (incidence 0.1%/annum)</td>
<td>4/5 SpA; 0/1 psoriatic tested</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rowe et al.</td>
<td>123</td>
<td>Selected prospective 40 months</td>
<td>100%</td>
<td>2 pre-HIV +/– 22</td>
<td></td>
<td>+</td>
<td></td>
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</tr>
<tr>
<td>Muñoz Fernández et al.</td>
<td>556</td>
<td>Retrospective 4yrs</td>
<td>100%</td>
<td>2 cases (0.5%)</td>
<td></td>
<td>0/1 reactive</td>
<td>−/+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monteagudo et al.</td>
<td>106</td>
<td>Cross-sectional</td>
<td>100%</td>
<td>0</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berman et al.</td>
<td>101</td>
<td>Cross-sectional</td>
<td>100%</td>
<td>10 cases (10%)</td>
<td>2 cases (2%)</td>
<td>5/8 reactive; 0/2 psoriatic</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medina-Rodríguez et al.</td>
<td>74 cases and 72 controls</td>
<td>Case–control 1 year + min 6 months f-up</td>
<td>51%</td>
<td>6 (8%) cases vs. 0 in controls</td>
<td>1 (0.6%) case</td>
<td>3/6 reactive</td>
<td>+</td>
<td></td>
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</tr>
<tr>
<td>Berman et al.</td>
<td>89 cases and 80 controls</td>
<td>Case–control 9/12</td>
<td>53%</td>
<td>10 cases (11.2%) vs. 2 (2.2%) controls</td>
<td>1 (0.6%) case</td>
<td>2/7 reactive</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casado et al.</td>
<td>74</td>
<td>Selected retrospective 7 years</td>
<td>100%</td>
<td>1 case (1%)</td>
<td>3 cases (4%)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Solinger and Hess</td>
<td>1100</td>
<td>Longitudinal, 7 years</td>
<td>100%</td>
<td>1 case (0.1%)</td>
<td>4 cases (0.4%)</td>
<td>−</td>
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<tr>
<td>Buskila et al.</td>
<td>52</td>
<td>Cross-sectional</td>
<td>100%</td>
<td>2 cases (3.8%)</td>
<td>3 cases (5.7%)</td>
<td>0/2 psoriatic</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marquez et al.</td>
<td>75</td>
<td>Selected prospective 3 years</td>
<td>100%</td>
<td>0</td>
<td>2 cases (2.6%)</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calabrese et al.</td>
<td>395</td>
<td>Prospective 1987–2000</td>
<td>100%</td>
<td>6 cases (0.14% incidence per annum)</td>
<td>3 cases (0.07% incidence per annum)</td>
<td>+</td>
<td></td>
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</tr>
<tr>
<td>Hochberg et al.</td>
<td>1133</td>
<td>Case–control 8 months + 5 year f-up</td>
<td>31% at baseline 42% at 5 year f/ up</td>
<td>2 cases (0.5%) vs. 4 (0.5%) in controls at start</td>
<td>0 cases</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Follow-up</td>
<td>Cases (Percent)</td>
<td>Control Cases (Percent)</td>
<td>Reactive</td>
<td>Notes</td>
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<tr>
<td>Clark et al.</td>
<td>1043</td>
<td>Case–control 1 year + f-up</td>
<td>39%</td>
<td>2 (0.5%) cases vs. 2 (0.3%) in controls</td>
<td>0 cases</td>
<td>-</td>
<td></td>
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</tr>
<tr>
<td>Chiowchanwisawakit et al.</td>
<td>178</td>
<td>Cross-sectional</td>
<td>100%</td>
<td>0</td>
<td>1 case (0.6%)</td>
<td>+</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Zhang et al.</td>
<td>98</td>
<td>Prospective</td>
<td>100%</td>
<td>0 cases</td>
<td>0 cases</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winchester et al.</td>
<td>65</td>
<td>Cross-sectional</td>
<td>100%</td>
<td>3 cases (4.6%)</td>
<td>2 cases (3%)</td>
<td>+</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Zhang et al.</td>
<td>&gt;1000</td>
<td>Selected prospective</td>
<td>100%</td>
<td>3 cases</td>
<td>4 cases</td>
<td>-</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Winchester et al.</td>
<td>65</td>
<td>Retrospective 27 months (SpA only)</td>
<td>26% of 31 cases SpA; 4% general population</td>
<td>14 (0.7%)</td>
<td>0 cases Not tested</td>
<td>+</td>
<td></td>
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<tr>
<td>Blanche et al.</td>
<td>36</td>
<td>Prospective 6/12</td>
<td>83% (of SpA)</td>
<td>8 cases (22%)</td>
<td>Not tested</td>
<td>?</td>
<td></td>
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</tr>
<tr>
<td>Blanche et al.</td>
<td>76</td>
<td>Prospective 16/12</td>
<td>79% (of SpA)</td>
<td>37 (4%)</td>
<td>?</td>
<td>?</td>
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<tr>
<td>Njobvu et al.</td>
<td>595</td>
<td>Prospective 29 month</td>
<td>87% pos</td>
<td>130 cases (22%)</td>
<td>0/30 tested</td>
<td>+</td>
<td></td>
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<tr>
<td>Njobvu and McGill</td>
<td>702</td>
<td>Prospective 44 months</td>
<td>87% pos</td>
<td>28 cases (4%)</td>
<td>13/100,000</td>
<td>+</td>
<td></td>
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</tr>
<tr>
<td>Njobvu and McGill</td>
<td>702</td>
<td>Selected prospective cohort 44 month + 14 month f/up</td>
<td>94% pos of 65 tested</td>
<td>170 (100%) only 71 studied, many pts from 1998</td>
<td></td>
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</tr>
<tr>
<td>Stein and Davis</td>
<td>595</td>
<td>Selected prospective cohort 4 years</td>
<td>n/a</td>
<td>24 cases</td>
<td>3 cases (4.7%)</td>
<td>0/13 tested</td>
<td>1 3</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Bileckot et al.</td>
<td>171</td>
<td>Prospective inpatients 1 year</td>
<td>29%</td>
<td>7 cases (4%)</td>
<td>Not tested</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Achuthan and Uppal</td>
<td>102</td>
<td>Cross-sectional</td>
<td>100%</td>
<td>2 cases (2%)</td>
<td>1 case (1%)</td>
<td>2/2 reactive</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krishnan et al.</td>
<td>29</td>
<td>Selected retrospective 4.5 years</td>
<td>100%</td>
<td>5 cases (17%)</td>
<td>1 case (3%)</td>
<td>3/ reactive</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Louthrenoo</td>
<td>100</td>
<td>Selected prospective 6 years</td>
<td>100%</td>
<td>8 cases (8%)</td>
<td>9 cases (9%)</td>
<td>3/8 reactive</td>
<td>+</td>
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*Rheumatologist read medical records but did not examine patients.*
be fewer cases.\textsuperscript{17,25} Other studies in intravenous drug users have reported similarly low estimates and the more common rheumatic manifestations were pain and musculoskeletal infections.\textsuperscript{21,32}

Prior to the HIV epidemic, there was a low prevalence of reactive arthritis in Africa most likely due to the rarity of the HLA B27 allele in Black African populations. The fact that enteric and urogenital infections were very prevalent in Africa, and would be expected to lead to increased occurrence of reactive arthritis, seemed to confirm the crucial role of specific HLA alleles in reactive arthritis. Since 1989, there have been reports from African countries of an increased incidence of reactive arthritis and that subjects affected were predominantly HIV-infected. For example, out of 65 Zambian patients with reactive arthritis, 61 (95\%) were HIV-infected.\textsuperscript{33} The picture is not clear-cut; however, as in Congo, seven patients were classified with reactive arthritis over 1 year among whom two (29\%) were HIV-infected, but in the same period, 32 cases of ‘HIV arthritis’ were reported.\textsuperscript{34} In Togo, a retrospective study of 2030 rheumatological patients over 27 months revealed only 14 patients diagnosed with reactive arthritis, none of whom were HIV-infected.\textsuperscript{35} These apparent discrepancies are difficult to explain but may result from several factors, including differences in diagnostic classification of the outcome (HIV arthritis vs. reactive arthritis) or mode of transmission of HIV.

In Asian studies, reactive arthritis appears rare. Two cross-sectional studies in China\textsuperscript{30} and Thailand\textsuperscript{29} reported no cases of reactive arthritis among 98 inpatients and 178 outpatients, respectively. The principal mode of HIV transmission in Asia is thought to be heterosexual, often involving commercial sex workers, but, because presumably of social stigma, the mode of transmission is frequently undisclosed. The apparent differences in the prevalence of reactive arthritis in Asia and Africa may be worthy of investigation since there is a high prevalence of arthritogenic pathogens on both Continents and, at least as far as is known, the main mode of HIV transmission is heterosexual. Therefore, reactive arthritis rates should be increasing similarly and the fact that this is not apparent in Asia raises the possibility that the reactive arthritis in Africa is linked to immunogenetic factors, rather than a link between HIV infection and environmental organisms. At present, however, the data are too complex and variable to draw any conclusions on the matter.

\textit{cART and reactive arthritis}

It is possible that reactive arthritis might be associated with the late stages of immunosuppression in HIV. This fits well with the low
prevalence of reactive arthritis in the US studies where most HIV patients were in the early asymptomatic phase.\textsuperscript{14,19,20} In the developed world since cART, there has been less published about reactive arthritis in HIV, which could suggest that HIV \textit{per se} does not increase the risk of reactive arthritis. However, another explanation is that high-risk sexual practices are more restricted since the HIV epidemic, resulting in reduced transmission of arthritogenic urogenital and enteric infections.\textsuperscript{19} Another possibility is that an effective cART regimen (i.e. a combination which achieves a rise in the CD4 count and a fall in the viral load) could affect the development and course of reactive arthritis. Indeed, one case has been reported of a patient with severe reactive arthritis in advanced HIV disease whose reactive arthritis resolved after commencement of a triple therapy cART regimen which produced significant improvement in the CD4 count\textsuperscript{36} when prior treatment with single and dual ARVs had not been effective. However, a comparison of rates of reactive arthritis among 80 HIV patients, 38 on unspecified single and dual therapy and 42 ARV-naïve showed no difference in the frequency.\textsuperscript{37} Furthermore, cases have been reported of new reactive arthritis emerging on commencement of cART, as a manifestation of immune reconstitution inflammatory syndrome (IRIS).\textsuperscript{11} 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.

\textbf{Psoriatic arthritis}

There have been several reports of mostly small- to medium-sized cohorts of HIV patients with psoriasiform rash and arthritis (Table 2).\textsuperscript{14–16,38,39} Rates of prevalence for psoriatic arthritis in HIV (PsA) range between 0.4\textsuperscript{14} and 5.7\%\textsuperscript{15}, which, compared with the prevalence of 0.25\% PsA in the general US population, suggested that HIV might increase the risk of PsA. However, the results of the two large US case–control studies\textsuperscript{19,20} found no cases of PsA among >2000 HIV-infected men, but it should be borne in mind that most of those infected were in the asymptomatic stage. One longitudinal study\textsuperscript{11} reported an incidence of 3 cases of PsA amongst 395 HIV-infected individuals over 11 years follow-up (incidence rate 0.07\%/annum), which approximates to the 0.05\% incidence rate reported in the general population. Along with a possible increased occurrence, the early studies suggested 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).\textsuperscript{1,16,39} Certainly, in one
study of three patients with ‘mild’ PsA, one patient was asymptomatic, one had lymphadenopathy only and only one had AIDS.\textsuperscript{15}

African studies performed before HIV infection suggested a very low rate of prevalence of psoriatic arthritis. However, since HIV, two studies have reported an increase in the occurrence of PsA\textsuperscript{33,40} (Table 2). Including 64 HIV-infected Zimbabweans with rheumatological symptoms, one study described three patients with severe, persistent PsA, all positive for HLA B17 and one for HLA Cw6.\textsuperscript{33} Over 44 months in Zambia, 28 patients with PsA were identified among 702 (4\%) patients with inflammatory arthritis: 27/28 (92\%) were HIV-infected, over half of whom were in the asymptomatic stage.\textsuperscript{40} In this study, PsA was the first presenting feature of HIV and most patients had extensive, symmetrical skin lesions with a simultaneous seronegative asymmetrical polyarthritis, typically affecting the lower limbs and causing radiographic erosions. 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. When cART becomes more available to HIV-infected patients in Zambia, it will be most informative to observe its effects on the occurrence of PsA.

In Asia, the evidence suggests a low prevalence of PsA. In China,\textsuperscript{30} a study of 98 consecutive HIV-infected inpatients reported no cases of PsA over 6 years. Similarly, low rates were reported in Thailand\textsuperscript{29} (point prevalence 0.6\%). One difficulty with this literature is that there is apparent overlap of the features of reactive and psoriatic arthritis in some studies.\textsuperscript{39,41,42} HIV patients can present with a pustular form of psoriasis indistinguishable from keratoderma blennorrhagica and with features common to reactive arthritis, psoriasis and PsA such as onychodystrophy, conjunctivitis, uveitis, enthesitis, balanitis and dactylitis. It is difficult to determine whether HIV infection is associated with a new type of psoriatic arthritis which overlaps with reactive arthritis (termed ‘undifferentiated spondyloarthropathy’ by some authors) or whether it concomitantly impacts the frequency of psoriasis and reactive arthritis. Additionally, HIV-infected patients with overlapping features of psoriatic arthritis and reactive arthritis are often positive for the HLA B27 allele.\textsuperscript{36} In accordance with this, most HIV-infected patients with PsA who tested negative for HLA B27 did not have overlapping features of reactive arthritis.\textsuperscript{1,15,16} Testing for HLA alleles typically associated with PsA (Cw6, B17) has been rarely performed (Table 2).

\textit{Psoriatic arthritis post-cART}

So far, there have been very few indications that cART changes the course of PsA in HIV, although there were early reports that AZT
improved skin psoriasis. In one Spanish study post-cART, three patients developed psoriatic arthropathy over 7 years of follow-up, none of whom were taking cART. Cases of IRIS psoriatic arthritis have been published after initiation of cART. Epidemiological studies post-cART have not often reported the severity of psoriatic arthritis. It is plausible that poorly controlled HIV infection is associated with the onset or exacerbation of psoriasis and psoriatic arthritis, but the evidence is inconclusive at present.

In terms of pathogenesis, it appears that the interaction between HIV and PsA depends on the overall balance between the various cells and cytokines of the immune system, rather than the absolute number of CD4+ and CD8+ T-cells. This is suggested by how different degrees of immunodeficiency, immune reconstitution and particular treatments seem to affect the course of disease. This may partly explain the two cases of IRIS described in which a rapid influx of CD4+ cells enabled by cART led to a rapid worsening of PsA. If psoriatic arthritis is indeed associated with HIV, then the mechanism behind this could be similar to that discussed for reactive arthritis. Autoimmune and infectious triggers have been implicated in the pathogenesis of psoriatic arthritis and could therefore be modulated in the context of immunodeficiency and infection. As with other spondyloarthropathies, HIV could be acting as a direct infectious trigger, as a gateway for persistent infections and/or as a dysregulator of autoimmunity.

Treatment of psoriatic arthritis in HIV

Conventional topical and systemic treatments for psoriasis and psoriatic arthritis have been reported as less effective in the context of HIV infection. In the case of methotrexate, most reports in the pre-cART era suggested that it may have a deleterious effect on patient health and in some cases, precipitate death. Since however, successful use of methotrexate in HIV-infected patients with severe psoriatic arthritis has been reported without opportunistic infections and the authors questioned whether methotrexate truly adversely affected the natural course of the HIV disease or instead reflected publication bias. Other disease-modifying drugs have now been used successfully as has the anti-TNFα antagonist infliximab.

Ankylosing spondylitis

Although ankylosing spondylitis (AS) is the most common form of seronegative spondyloarthritis in the Western world, there have
been few reports of AS coexisting with HIV infection. There have been three case reports (all of whom were HLA B27-positive) and in all three cases, HIV was diagnosed 10–15 years after the onset of AS and did not alter its course. The authors hypothesized that since the CD4+ depletion inherent to HIV infection does not affect the course of AS, then these cell types may not be involved in the pathogenesis. In those studies carried out in Asia, no cases of AS were reported amongst HIV-infected patients. In Africa, as expected, given the low prevalence of the HLA B27 allele, cases of AS are rare in the general population, and even rarer in HIV-infected individuals, as opposed to the other spondyloarthropathies. Of the 16 reported patients with AS in Togo and Zambia, none were HIV-infected. The largest study more recently conducted in Zambia again showed a relative scarcity of AS compared with reactive arthritis.

Taken together, these data might suggest that AS is uncommon in HIV. However, it must be borne in mind that the diagnostic criteria for AS rely upon presentation with features of inflammatory back pain, HLA B27 positivity and radiographic sacroiliitis. Among 14 Zambian patients presenting with spontaneous sacroiliitis when compared with seven patients presenting with sacroiliac strain (secondary to trauma), the patients with sacroiliitis had a positive clinical stress and raised ESR, but normal radiographs. Four of these 14 went on to develop polyarthritis and enthesitis at follow-up and could have been classified as undifferentiated spondyloarthropathies. Longer 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.

**Rheumatoid arthritis**

Early case reports suggested that patients with established rheumatoid arthritis (RA) experienced clinical improvement after the development of immunodeficiency caused by HIV. This fuelled speculation that depletion of CD4+ helper/induced lymphocytes might be producing clinical improvement and that this could potentially inform the aetiology-pathogenesis of RA. Since then however, erosive seronegative symmetrical polyarthritis has been reported in HIV as has seropositive destructive RA emerging de novo in a patient with HIV infection with a depleted CD4+ count not taking cART. After the emergence of active RA, cART was commenced and 2 weeks later, when his CD4
count improved, he developed rapid and significant increase in joint pain and required oral glucocorticoids, sulfasalazine and hydroxychloroquine.\textsuperscript{52} This case seemed to contradict the assumption that had been made about the relationship between CD4\textsuperscript{+} count and activity of RA. However, it is possible that the flare 2 weeks after cART was in fact IRIS. A Zimbabwean study reported 8 out of 64 patients with arthritis and prevalent HIV infection with a symmetrical polyarthritis affecting the hand and wrist joints, 3 of whom were positive for rheumatoid factor and 1 of whom developed radiographic erosions.\textsuperscript{33} The authors postulated that some of these eight patients had true RA and that others had a ‘symmetrical rheumatoid-like arthritis occurring with HIV’.

It is possible that case attribution has been affected by the early reports that RA could not co-exist with HIV infection. For example, Cuellar\textsuperscript{53} described ‘a polyarticular erosive form usually confused with rheumatoid arthritis’ in his review of the rheumatic manifestations of HIV in 1998. Ornstein \textit{et al.}\textsuperscript{54} suggested that these early reports led to uncertainty in the rheumatological community and bias against labelling an inflammatory symmetrical polyarthritis, affecting the hands and wrists as RA in the usual way. Subsequent case reports have also been published and currently, it appears that RA can co-exist with HIV infection and may ante-date or post-date the infection. If it occurs in HIV-infected patients, it can be difficult to treat as conventional treatment of RA requires immunosuppression, but data are accumulating to suggest that sulfasalazine and hydroxychloroquine can be used safely and that methotrexate and biologic therapies (anti-TNF\textalpha) may be used with careful monitoring.

\textit{HIV arthritis}

Several publications have reported a prevalence estimate up to 12\% for ‘HIV arthritis’.\textsuperscript{13,16,17,29,30,55,56} Typically described as a non-erosive oligoarthritis mainly involving the lower limbs, it is not associated with enthesitis, HLA B27 or mucocutaneous involvement. It is also described as self-limiting usually in <6 weeks. Clearly, this entity, if it is unique to HIV infection, shares characteristics with other types of seronegative arthritis and its ‘diagnostic’ criteria apply only when arthritis shows no diagnostic features to classify it as AS, PsA or reactive arthritis. With so much doubt about its existence as a ‘discrete’ entity, it is unsurprising that there are few data as to the effect of cART on the incidence of this condition. More, carefully controlled studies with pre-defined diagnostic criteria are indicated.
Gout

It has been estimated that 0.5% of HIV/AIDS patients develop gout annually, but this estimate pre-dates the widespread use of cART. It is increasingly recognized that hyperuricaemia occurs in association with several anti-retroviral therapies, particularly PIs including ritonavir, didanosine at high doses and stavudine. It seems likely therefore that the incidence of gout might be increased in the cART era, but, to date, the relevant epidemiological studies have not been performed.

Septic arthritis

Septic arthritis is more common in immunodeficiency and therefore a high incidence right be expected in HIV. Interestingly, the results of HIV cohort studies find a relatively low risk of septic arthritis and that when it occurs, there is no clear relationship with CD4+ counts. Opportunistic organisms are implicated when CD4+ counts <200 but more traditional organisms (staphylococci and streptococci) when CD4+ counts >200. The most significant risk factor for septic arthritis is intravenous drug use.

Vasculitis and connective tissue diseases

Systemic lupus erythematosus, Sjogren’s syndrome, polymyalgia rheumatica, temporal arteritis and other vasculitis, polymyositis, sarcoidosis, Behçet’s disease, auto-antibody formation, cryoglobulins, immunoglobulin abnormalities and circulating immune complexes have all been reported in HIV. Most evidence pre-dates cART. Peculiar to HIV is the Sjogren’s-like syndrome diffuse infiltrative lymphocytosis syndrome (DILS) in which CD8+ lymphocytosis and CD8+ infiltration cause parotid and lacrimal gland swelling, sicca symptoms and extra-glandular manifestations. Given the relative rarity of most of these conditions, changes in the epidemiology pre- and post-cART have been difficult to confirm. DILS was reported to respond to cART and its incidence has apparently declined since cART, although we have not identified epidemiological evidence of this. Paradoxically, cases of many of the connective diseases have been reported after commencement of cART (IRIS). Longer-term controlled clinical trials will be required to evaluate the effects of cART on connective tissue diseases.
Conclusions

A modern-day pandemic, untreated HIV is associated with immunosuppression. There is considerable evidence that HIV immunosuppression causes musculoskeletal pain and several articular and multisystem connective tissue diseases. Since cART, opportunistic infections and malignancies have been considerably reduced, but normal immune function is not fully restored. At present, it is unclear what effect cART has had on most rheumatic manifestations and further controlled studies are required. A feature of this literature is incomparability due to diverse diagnostic classification systems. Future research must be standardized to internationally recognized diagnostic classification criteria so as to facilitate developments in this field. Finally, HIV-infected patients may need treatment of inflammatory autoimmune conditions with immunosuppressants. Safety and efficacy data for this approach are urgently required.

References


