Human Immunodeficiency Virus Related Reactive Arthritis in Zambia

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ABSTRACT. ***Objective.*** To characterize the clinical, radiological, and diagnostic features of reactive arthritis (ReA) in indigenous Black Zambians with human immunodeficiency virus (HIV) infection.

Methods. Consecutive patients attending an arthritis clinic over a 5-year period were studied prospectively. Those who satisfied diagnostic criteria for ReA were analyzed.

Results. In total, 170 patients satisfied the ESSG criteria for ReA; 71 (45 men, 26 women) had one or more extraarticular manifestations; 30% had enteroreactive and 14% uroreactive disease. Only 59% of patients had the diagnostic features of ReA at presentation. The initial diagnosis was undifferentiated spondyloarthropathy (uSpa) in 20%, other ReA in 14%, and "arthritis alone" in 7%. Of 65 (42 men, 23 women) patients tested, 94% were HIV-positive (91% men, 100% women). In those with HIV, the arthritis was predominantly polyarticular, lower limb-predominant, and progressive; 58% of 33 with persistent disease had erosions of foot and/or hand joints (average disease duration, 24.4 mo); 6 of 10 showed early radiological spine or sacroiliac joint changes (average duration 47.7 mo). Anterior uveitis occurred in 33% of patients, while keratoderma blenorrhagicum and stomatitis occurred in 14.3% and 9.5%, respectively, of patients with enteroreactive ReA. Uroreactive ReA was more common in women. There were no significant differences in the clinical, diagnostic, or radiographic features between men and women or between those with or without a known preceding trigger.

Conclusion. HIV associated ReA in Black Zambians frequently follows an accelerated course with a strong tendency to relapse, develop early erosions and joint deformity, and become chronic. The clinical, diagnostic, and radiographic features are indistinguishable from those described in the conventional (HLA-B27 related) disease, although our HIV-positive patients have a high overall frequency of uveitis, keratoderma, and onycholysis. (J Rheumatol 2005;32:1299–304)

Key Indexing Terms:

REACTIVE ARTHRITIS | HUMAN IMMUNODEFICIENCY VIRUS | INFECTION
SUB-SAHARAN AFRICA | SPONDYLOARTHRITIS | ZAMBIA

Despite a high prevalence of gastrointestinal and sexually transmitted diseases associated with reactive arthritis (ReA) in sub-Saharan Africa, this disorder was until recently distinctly uncommon[1]. This low prevalence has been attributed to the virtual absence of the B27 gene in Black populations[2,3]. The epidemic of human immunodeficiency virus (HIV) infection across the subcontinent has, however, brought in its wake a growing number of reports of a link between HIV and spondyloarthropathies (SpA)[4-7]. Nevertheless, there is little information on clinical, radiological, and prognostic factors of specific syndromes. Available data are largely cross-sectional, and therefore do not fully account for changes in diagnostic features that may occur with time. As such, the full diagnostic characteristics and prevalence of specific SpA remain incompletely defined. There have also been no studies evaluating the influence of gender and infectious triggers in clinical manifestations of these syndromes. Our initial report[7] included 130 patients with ReA, 48 of whom had associated extraarticular features. We have since encountered 71 such patients. This is a descriptive report of the clinical, radiographic, and diagnostic features of 61 HIV-positive patients.

MATERIALS AND METHODS

Consecutive patients attending an outpatient rheumatic disease clinic at the University Teaching Hospital (UTH), Lusaka, between April 1994 and December 1997 were studied prospectively up to February 1999. Demographic information, history of venereal exposure or trauma, personal and family histories of arthritis, and duration of joint symptoms were recorded. A detailed history was obtained at initial presentation and on subsequent reviews regarding joint symptoms, heel pain, back pain and stiffness, mucosal and skin lesions, symptoms of acute anterior uveitis, conjunctivitis, urethritis, and diarrhea. Examination paid special attention to the painful part and also to peripheral joints, spine, the sacroiliac joints and other entheses, external genitalia, eyes, and buccal mucosa. At initial consultation, patients were classified according to the criteria of the European Spondylarthropathy Study Group (ESSG)[8]. The diagnosis of ReA was given to those in whom a seronegative asymmetrical peripheral arthritis was preceded by an episode of enteric or urogenital infection within the previ-

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ous 4 weeks and/or accompanied by one or more of these extraarticular features: urethritis/cervicitis, inflammatory eye disease, and mucocutaneous disease (balanitis, oral ulceration, keratoderma blenorrhagicum).

Patients with arthritis ≥ 4 weeks' duration who did not fulfil the criteria of a recognized rheumatic disorder were diagnosed as having "arthitis alone"[7]. The diagnosis was revised in the course of followup to match the clinical picture.

Arthritis and enthesitis were diagnosed in the presence of joint or enthesial tenderness/and or swelling. Sacroiliitis was diagnosed when buttock pain was accompanied by a positive sacroiliac stress test.

Conjunctivitis was diagnosed on history and/or examination, and anterior uveitis by slit lamp examination and/or the presence of its sequelae.

Microbiological examinations were performed on stool, urethral or cervical smears, and synovial fluid as appropriate.

Radiographs of the hands/feet, spine, and sacroiliac joints were obtained in those with persistent symptoms or clinical abnormality at these sites.

A duplicate, anonymous and unlinked test for HIV (ELISA) was carried out on all consenting patients. Staging of HIV infection was by the World Health Organization (WHO) clinical criteria[9].

T cell subsets were analyzed using flow cytometry.

Student t test and the differences in proportions with 95% confidence intervals (95% CI) were used to compare characteristics as appropriate.

The study was authorized by the hospital's research and ethics committee.

RESULTS

Table 1 shows the diagnoses in 702 patients who presented during the period of study. Of 170 who satisfied the ESSG criteria for ReA, there were 71 who had at onset or developed later one or more extraarticular lesions associated with ReA. Because dysentery/diarrhea are so common in the African AIDS setting, we decided to include in this analysis only those with one or more of these extraarticular lesions.

All 71 patients were sexually active in heterosexual relationships; 41 were married, 22 single, 5 divorced, and 3 widowed. None had received a blood transfusion prior to the onset of arthritis or other HIV related clinical problems. Six patients refused the HIV test and of the 65 tested, 61 were positive (95%). The 4 HIV-negative patients were all < 21 years old; their only extraarticular lesions were conjunctivitis (n = 2) and urethritis (n = 2); none exhibited erosive, relapsing, or persistent disease during the period of observation. In all 4, arthritis remitted within 2–6 months (mean 3.7 mo) of onset. These patients were excluded from further consideration.

Forty-two patients had an extraarticular lesion(s) at presentation, and 29 developed one or more later. Their initial diagnosis before revision was 14 undifferentiated SpA, 5 arthritis alone, and 10 other ReA.

Table 2 shows the characteristics of 61 HIV-positive patients. There was no difference in frequency of the various extraarticular lesions apart from a male preponderance of keratoderma and onycholysis. Men and women were otherwise similar with respect to age, disease duration, and frequency of recurrent disease.

Table 3 shows the diagnostic and extraarticular features of 31 (16 men, 15 women) patients with a known preceding infectious trigger. Urogenital infectious triggers occurred more commonly in women.

The pattern of joint involvement at presentation was lower limb-predominant, asymmetrical polyarthritis. The mean joint count was 13.2 (range 1–54); 3 patients (2 men, 1 woman) had monoarthritis, 18 (12 men, 6 women) had 2–5 joints affected, and 40 (24 men, 16 women) had ≥ 5 joints affected.

Enthesitis was present in 30 (49%) patients at presentation and developed during followup in 18 more (Table 1). Severe and persistent or recurrent polyenthesitis (> 5 sites affected) was the modal pattern of involvement. Heel pain

Table 1. Diagnoses of 702 patients who presented during the study.

Diagnostic Group	N (% of total)
Undifferentiated SpA	207 (29.5)
Reactive arthritis	170 (24.2)
Post-dysenteric	122
Uroreactive	11
Unknown trigger with extraarticular features	37
Arthritis alone	202 (28.8)
Rheumatoid arthritis	45 (6.4)
Gout	36 (5.1)
Psoriatic arthritis	28 (4.0)
Other	14 (2.0)
Total	702 (100)

Table 2. Characteristics of 61 HIV-positive patients.

Features	Male, n = 38	Female, n = 23
Characteristics at presentation		
Mean age, yrs, ± SD	33.24 ± 7.74	29.70 ± 9.28
Mean disease duration, mo ± SD		
Current episode	5.47 ± 9.24	3.62 ± 3.95
Whole duration	16.01 ± 18.85	9.25 ± 12.63
First ever episode, n	26	18
Duration, mo ± SD	6.56 ± 10.98	3.82 ± 4.33
Extraarticular lesions		
Uveitis*	9	11
Conjunctivitis	23	14
Urethritis	18	10
Balanitis	13	n/a
Prostatitis	3	n/a
Vulvitis	n/a	2
Cystitis	1	2
Keratoderma	7	1
Stomatitis	2	3
Onycholysis	7	0
Enthesitis	33	15
Dactylitis	8	8
Heel pain	19	9
Aortic incompetence	2	1
Mitral valve prolapse	1	1
Pericarditis	1	1
History of palpitations	2	6

* 12 were among 43 patients with their first-ever episode of arthritis; 8 were among the 18 with recurrent arthritis.

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Table 3. Features of 31 patients with a preceding infectious trigger.

Preceding Trigger	Enteric Infection		Urogenital Infection	
	Male, n = 13	Female, n = 8	Male, n = 3	Female, n = 7
Conjuctivitis	6	6	3	3
Urethritis/cervicitis	9	1	3	7
Acute uveitis	2	3	2	3
Balanitis/vulvitis	5	2	0	0
Prostatitis	0	n/a	0	n/a
Cystitis	0	0	0	0
Keratoderma	2	1	0	0
Stomatitis	2	0	0	0
Erythema nodosum	0	1	0	0
Enthesitis	6	6	2	3
History of previous episode	5	6	2	2

was due to Achilles tendinitis and/or plantar fasciitis or calcaneal periostitis. The pattern of involvement and clinical course of both arthritis and enthesitis were similar in men and women.

The onset of uveitis was generally delayed: 4.8 months (range 1 week to 10 mo) among those with first-ever episode of arthritis and 6.9 months (range 2–13 mo) among patients with recurrent arthritis.

Twenty-one patients experienced an episode of diarrhea within 4 weeks prior to the onset of their arthritis. This was usually a dysenteric-like illness with blood and mucus. *Shigella flexneri* is endemic in Lusaka at present. Twenty-three patients with no preceding history of diarrhea reported at least one episode of diarrhea subsequent to the onset of arthritis, including 8 of 10 (5 men, 3 women) patients with uroreactive disease, and 15 (13 men, 2 women) patients with no known preceding trigger. In 8 such patients (5 men, 3 women) the diarrhea was brief, but recurrent, and dysenteric-like (blood and mucus, pathogen-negative).

Urethritis occurred in 28 patients as follows: preceded arthritis in 10 patients (3 men, 7 women), occurred in 10 of 21 (9 men, 1 woman) with post-enteric disease, and occurred in 8 of 30 (6 men, 2 women) of those without a known trigger. In this group, the frequency of uveitis was 8/28 (4 men, 4 women); balanitis 6/18 men; keratoderma blenorrhagicum 4/28 (all men); and stomatitis 3/28 (1 man, 2 women). These frequencies are similar to those among patients who never experienced urethritis (n = 33). In 4 (1 man, 3 women) with uroreactive disease, *Neisseria gonorrhoea* was isolated from urethral and cervical smears.

Table 4 shows the clinical and HIV status of 44 patients at last observation. Seventeen patients were lost to followup. About two-thirds of patients responded symptomatically to treatment with a nonsteroidal antiinflammatory drug (usually indomethacin or ibuprofen) and local or systemic steroids for flares. However, the remainder continued to experience severe exacerbations, and subject to availability were treated with either sulfasalazine or chloroquine. We have published results of the beneficial effects of sulfasalazine in HIV related SpA[10]. Advanced HIV clinical disease (WHO stage 3 or 4) was associated with spontaneous amelioration of arthritis. Six patients died during the period of observation. All had deteriorated to stage 4 HIV disease, and the inflammatory component of their arthritis had long gone into remission at the time of their death.

At presentation, 48 (30 men, 18 women) were in HIV clinical stage 1, 5 (3 men, 2 women) in stage 2, and 8 (5 men, 2 women) in stage 3.

The mean hemoglobin concentration was 13.1 ± 0.9 g/dl, platelet count 405 ± 70 × 10^9/l, white blood cell count 6200 ± 340/mm^3, total lymphocyte count 1876 ± 97/mm^3, and erythrocyte sedimentation rate 114 ± 38.5 mm/h.

The mean CD4 count in 29 (18 men, 11 women) patients was 250.3 ± 201.5 cells/l. There was no significant difference in the counts of men (276.7 ± 222.7 cells/l) and women (191.0 ± 152 cells/l). None of 53 patients tested positive for rheumatoid factor or antinuclear antibodies (n = 8).

Radiographs of hands and feet were available for 33 patients (21 men, 12 women). Fourteen patients showed soft tissue swelling with variable degrees of periarticular osteoporosis; average disease duration at radiological examination was 4 months (range 1–18 mo).

Nineteen (12 men, 7 women) patients showed erosive changes in the wrists, tarsal, and small hand and foot joints (Figure 1). Other changes were periostitis, subluxation, and ankylosis. The average duration of disease was 24.4 months (range 5–68 mo).

Ten patients (6 men, 4 women) had radiographs of the spine and sacroiliac joints; 5 (3 men, 2 women) showed early spinal changes, consisting of vertebral squaring (1 man, 2 women), isolated lateral and/or anterior syndesmophytes (2 men), and anterior spinal erosions (Romanus lesions; 1 man, 1 woman). Three (2 men, 1 woman) patients, including 2 with spinal changes, had asymmetrical sacroiliac joint changes — sclerosis and widening (1 man, 1 woman), and erosions with irregular narrowing (1 man). Average duration of disease was 47.7 months (range 30–60 mo).

Six men showed erosions at the calcaneal insertions of

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Table 4. Clinical and HIV status of 44 patients at last observation (17 patients were lost to followup).

Disease Activity	No. of Patients (M:F)	Followup Duration, mo ± SD	Whole Duration of Arthritis, mo ± SD	WHO HIV Clinical Stage, n			
				1	2	3	4
Remitted or > 50% improvement, but still needing NSAID	10 (7:3)	3.9 ± 4.07	17.70 ± 14.13	5	3	2	0
Remitted, not needing NSAID for ≥ 2 mo	12 (8:4)	22.33 ± 10.71	37.17 ± 18.82	5	2	3	2
Unchanged or worsening*	16 (9:7)	9.13 ± 11.52	20.00 ± 18.28	12	3	1	0
Died	06 (4:2)	12.18 ± 11.47	25.93 ± 18.88	0	0	0	6

NSAID: nonsteroidal antiinflammatory drugs.

the Achilles tendon and/or plantar fascia; 3 (1 man, 2 women) patients had calcaneal spurs (Figures 2 and 3).

DISCUSSION

It is the characteristic extraarticular features of ReA that allow ease of recognition and distinction from other forms of arthritis. These features were exhibited by about 40% of those patients who satisfied the ESSG criteria for ReA in our clinic. These patients would therefore have satisfied the criteria for Reiter's disease. However, our sentiments are with those who favor discarding the eponym in favor of ReA[10].

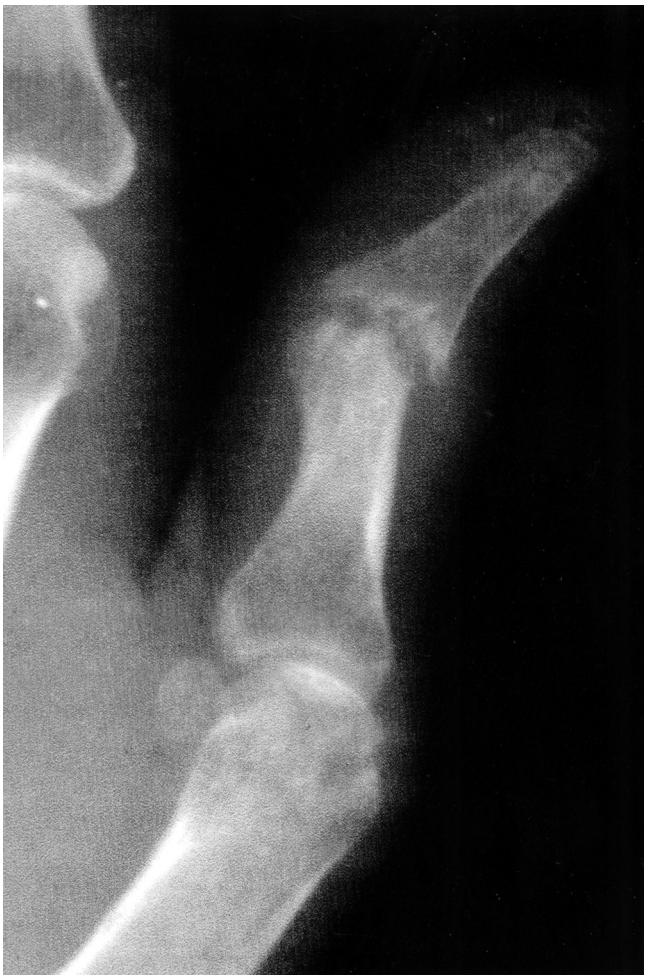

Figure 1. Erosion of 1st distal interphalangeal joint.

African literature had previously emphasized the rarity of all SpA, including ReA, among indigenous Black Africans[11-15]. In recent times HIV associated arthritides have become a common reason for rheumatological consul-

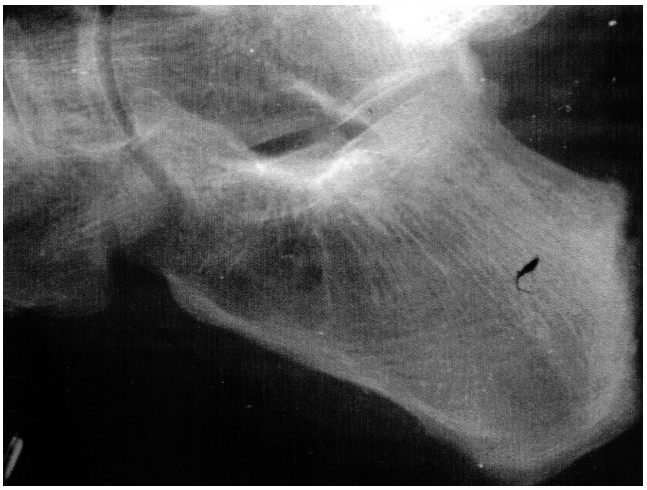

Figure 2. Fusion of midtarsal joints, "fluffy" calcaneal spur.

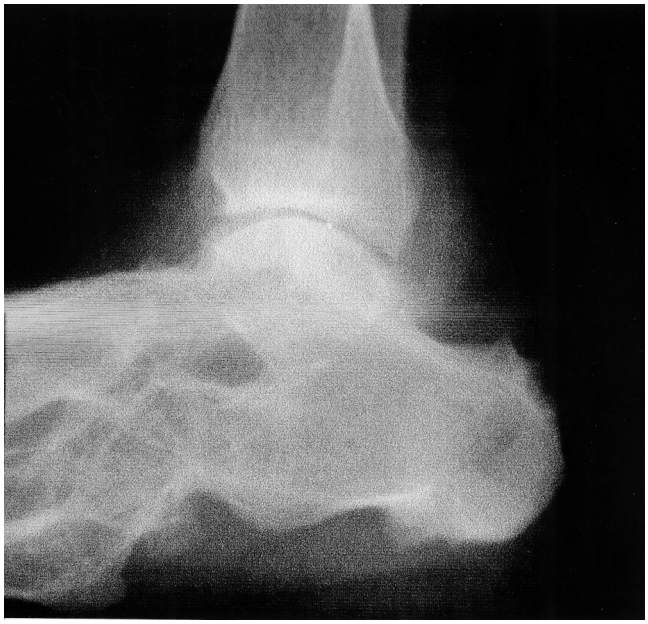

Figure 3. Achilles insertional enthesitis.

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tation in regions of the subcontinent with a high HIV prevalence[7,8,16-18]. Despite these reports, however, the diagnostic, clinical, and prognostic characteristics of specific HIV associated SpA are only now beginning to be described[18].

Our study is the largest single prospectively collected cohort of Africans with ReA, and as such allows us to determine the clinical and diagnostic characteristics in HIV infected African men and women and to evaluate the influence of HIV infection on its prevalence.

The high overall prevalence of HIV (94%) in patients with ReA echoes the overwhelming association between HIV and certain other SpA noted previously in the subregion[7,8,18], and further highlights the rarity of this particular SpA in a non-HIV-infected indigenous African population.

This cohort of Africans expresses many of the features of ReA described in Caucasians who are B27-positive, with and without HIV infection, namely, the pattern of clinical and radiological joint involvement and prevalent extraarticular lesions[19,20], a weak overall predominance of males[21], and the occurrence of urethritis as a complication of entero-ReA[22,23]. However, the outstanding clinical feature in our patients is the tendency for the arthritis to recur (30% at first presentation and 23% during one year of followup) and become chronic from an early stage. This is quite unlike anything described to date in Black Africans. While Caucasians with "conventional" ReA arthritis show a higher frequency of recurrence with longer followup, it is not of the frequency or severity witnessed in our cohort[23-25].

Nevertheless, there are accounts of Caucasians who are HLA-B27-positive and with HIV infection who develop severe unremitting disease similar to that experienced by many of our patients[20].

The variety and frequency of certain extrarticular features in our patients broadly reflects the pattern observed in other racial groups. However, uveitis occurred with around twice the frequency for both first episode and recurrent disease than recorded elsewhere[23,24], reflecting the accelerated pace at which ReA progresses in this group of HIV infected patients.

The hitherto low level of reporting of SpA in Africa has partly been attributed to a lack of awareness and proper investigative facilities. Thus, where patients designated as having "acute tropical polyarthritis"[26] have been thoroughly investigated, it has been possible to revise the diagnosis to gonococcal arthritis, ReA, or infective arthritis[27]. Further, since ReA is an evolving disease in which all diagnostic features may not be present when patients are first seen, cross sectional or short term observational studies from which much of the information on Africa is derived increase the likelihood of misclassifying some patients. It is noteworthy in this respect that more than 40% of our patients could not be classified as ReA at presentation. This observation, paired with the observation in this cohort and in our previous report[7] that HIV-negative patients with undifferentiated arthritis (arthritis alone) show no progression, suggests that the HIV infected state transforms an arthritis not uncommon in the African setting to develop specific SpA features.

The remarkable association of conventional ReA with the HLA-B27 antigen is sustained in cases of HIV related ReA in Caucasians[19]. No such association has been noted in Africans with either form of ReA[1,7,8]. The role of B27 in predisposing to severe disease and to distinctive SpA extraarticular features is well documented[22]. In this scenario the rarity of ReA in African populations at low risk of the disease immunogenetically, the lack of association with B27 in those in whom ReA occurred, and the comparatively milder clinical character of the disease[1,10] have hitherto supported the role of B27 in determining the full clinical picture of SpA. In the light of current observations and previous reports in the subregion[7,8,18], alternative pathogenetic explanations to account for HIV related SpA are necessary.

It has been suggested that other class I genes may become relevant in the HIV infected state owing to upregulation[28]. Of particular interest in HIV infected Africans are the cross-reactive antigens (B7-CREG). HLA-B7 has been found as frequently in Southern African populations as in some Caucasian populations[2,29,30]. Stein and Davis[6] found B7 in 31% of 13 HIV infected Zimbabweans with ReA. This prevalence is significantly higher than that of 14% in 146 blood donors[2], but lower than the 60% found among 10 HIV-negative ReA patients[1], thus suggesting that B7-CREG may not confer greater susceptibility in the HIV infected patient compared to the HIV-negative individual. We have recently typed 54 HIV-positive Zambian SpA patients and 100 HIV-positive controls[31]. Of the B7-CREG, only B7 was found, with a frequency of 11% among SpA patients and 16% in the control groups. However, there was a statistically significant association with HLA-B*5703 (split product of B17). The prevalence was 54% in patients with SpA compared to 9% in controls. While the B*5703 allele therefore appears to predispose to SpA in the upregulated HIV infected state in our patients, further studies are required to unravel the complex biochemical, bacteriological, and immunological interactions associated with ReA and other spondyloarthropathies in Black Africans.

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