

THE PATTERN OF INFLAMMATORY RHEUMATIC
DISORDERS IN A CENTRAL AFRICAN TEACHING
HOSPITAL
WITH EMPHASIS ON HIV-ASSOCIATED
ARTHRITIDES

DR. PANGANANI DALISANI NJOBVU, (B.Sc.(Hb), MB.CH.B
Department of Internal Medicine
University Teaching Hospital
LUSAKA.

THIS DISSERTATION WAS SUBMITTED FOR THE MASTER OF MEDICINE
(M.MED) DEGREE IN INTERNAL MEDICINE, UNIVERSITY OF ZAMBIA.

SEPTEMBER, 1997

A P P R O V A L

This dissertation of **Panganani Dalisani Njobvu** is approved as fulfilling part of the requirements for the award of the degree of Master of Medicine by the University of Zambia.

Signatures

Date

~~Present~~
.....
.....
.....

12/ 9 / 1996.....
18/04/97.....
.....
.....

CONTENTS

	PAGE
* ACKNOWLEDGEMENTS	(i)
* DECLARATION	(iii)
* LIST OF TABLES AND FIGURES	(vi)
* LIST OF ABBREVIATIONS AND DEFINITIONS	(vii)
* SUMMARY	1
* INTRODUCTION	4
* OBJECTIVES	21
* PATIENTS AND METHODS	22
* RESULTS (OVERVIEW)	31
— PART 1: ENTHESITIS ALONE GROUP AND SERONEGATIVE ARTHRITIS	35
A: ENTHESITIS ALONE GROUP	35
B: SERONEGATIVE ARTHRITIS (GENERAL)	37
C: SERONEGATIVE ARTHRITIS: SYNDROMES	43
D: SERONEGATIVE ARTHRITIS: HIV ASSOCIATION	59
E: SERONEGATIVE ARTHRITIS: CLINICAL FEATURES	63
F: SERONEGATIVE ARTHRITIS: CLINICAL FEATURES VIS-A-VIS HIV SEROSTATUS	81
— PART 2: OTHER CONDITIONS	90
— SULPHASALAZINE THERAPY	98
— DISCUSSION	102
— CONCLUSIONS	111
— RECOMMENDATIONS	112
— REFERENCES	121
— APPENDICES I TO VII: RADIOGRAPHIC FEATURES:	130

ACKNOWLEDGEMENTS

I am grateful to all those persons who have supported me in the past two years and helped make this research effort a reality. The all important turn-around came in 1993—special thanks to Professor J.O.M Fobee (Head of Department of Medicine, U.T.H.) and Dr. Paul McGill (Consultant Rheumatologist of Stobhill NHS Trust, Glasgow,

Scotland) for arranging an orientation and teaching programme in Rheumatology for me and for their supervisory role throughout the time of the study.

Many perceptive and helpful criticisms of my research protocol also came from Professor John E. Jellis (Professor of Orthopaedics, U.T.H.) who himself has done some pioneering work on the problem of HIV - associated arthritis in Zambia and set up the arthritis clinic in 1991.

I also owe a great debt of gratitude to the JICA team and the Virology laboratory staff without whom it would not have been possible to have so many patients tested. In particular, I thank Dr. Oshitani and Dr. Mpabalwani for availing their laboratory services to me, and Mr. Changwe who performed all the serological tests and ensured that the results reached me.

The volume of work that I had to tackle meant that I had to work long hours. I thank my wife and children for understanding why I had to be neglectful of them and for weathering the hard days when I could not be available for them.

I also wish to express my sense of appreciation and gratitude to the clinic nurses and clerks for lining up the appointments and for their invaluable assistance during the clinic hours.

Finally, I thank the patients for teaching me so much. From them I have learnt not only the details of their disease but they have also enabled me gain full appreciation of the dauntless spirit of men to get rid of the adversity of pain and discomfort regardless of the underlying cause. My greatest lesson has come from the HIV infected patients who had sought knowledge of their HIV status. This knowledge did not dampen their desire to defeat their pain and they were as full of praise and thankfulness as everyone else for a remedy that produced favourable results. This often reminded me of the limitations of medical science to cure disease but also reminded me of the countless avenues for soothing pain and discomfort available to the Doctor, which often is the only thing we can do for those who need us most and count on us for a miracle - the terminally ill and those with incurable disease.

DECLARATION

I hereby declare that this piece of work is original and has not been published before. However, partial analyses at various stages have been presented at various local and international meetings as follows:-

A: LOCAL MEETS

- (i) Department of Medicine's weekly clinical meeting, University Teaching Hospital on 21/02/95.
- (ii) Weekly clinical meeting of the Maina Soko Military Hospital on 11/07/95.
- (iii) Two oral presentations at the Resident Doctors Association's "first Scientific Meeting in Lusaka on 29 and 30 September, 1995 entitled:
 - *"The diagnostic implications of enthesitis and pattern of joint involvement in HIV-associated arthritis in black Zambians". and
 - *"Seronegative spondylarthropathies: perspectives in Zambia".
- (iv) A poster presentation at the Zambia Medical Association's Annual General Assembly on 4th April, 1996 in Lusaka, entitled:
 - *"Radiographic Manifestations of Human Immunodeficiency Virus-associated arthritis".

B: INTERNATIONAL MEETINGS

- (i) A poster presentation at the British Society of Rheumatology's Heberden Round, 13-15 September, 1995 in London, entitled:
* "Arthritis associated with HIV infection in Zambia".
- (ii) *Two oral presentations at the 2nd African League against Rheumatology's congress, 15-18 October, 1995 in Tunis, Tunisia, entitled:
* "Efficacy and safety of sulphasalazine on HIV arthritis". and,
* "Seronegative arthritis and HIV infection in Lusaka, Zambia".
- (i) 
- (iii) Two poster presentations at the 8th Pacific League against Rheumatology's congress in Melbourne, Australia, 21-26 April, 1996 entitled:
* "Rheumatic disorders at a Zambian Teaching Hospital", and
* "Efficacy of sulphasalazine in HIV arthritis".

Owing to continuing controversies and misconceptions about the association between HIV and Rheumatic disorders (apparent at international meetings and in current literature) and in order to draw attention to our experiences here, we have done a Zambian review of the growing contribution of HIV-associated arthritis to the prevalent rheumatic disorders from the late 1980's to the end of 1995. The paper is co-authored by Professor J.O.M. Pabee (my supervisor), Professor J.E. Jellis (Department of Orthopaedics U.T.H.), and Dr. P.E. McGill (Rheumatologist Stobhill NHS Trust, Glasgow, "Scotland"). We have sent it to the British Journal of Rheumatology for consideration for publication.

Finally, I wish to further state that this Dissertation shall be the property of the University of Zambia and that no part of it may be published without their prior permission.

Signature of Student:



Signature of Supervisor:



LIST OF TABLES AND FIGURES

		PAGE
TABLE	I: DIAGNOSTIC GROUPS	33
TABLE	II SERONEGATIVE ARTHRITIS SYNDROMES	38
TABLE	III CLINICAL FEATURES OF PATIENTS WITH POSSIBLE ANKYLOSING SPONDYLITIS	45
TABLE	IV PATTERN OF JOINT INVOLVEMENT	55
TABLE	V FREQUENCY OF ENTHESITIS	58
TABLE	VI CLINICAL FEATURES OF HIV POSITIVE AND HIV NEGATIVE PATIENTS WITH SERONEGATIVE ARTHRITIS	69
TABLE	VII ENTHESOPATHIC LESSIONS IN HIV NEGATIVE PATIENTS	75
TABLE	VIII UROGENITAL, OCULAR AND OTHER EXTRA-ARTICULAR LESSIONS	76
TABLE	IX THERAPEUTIC STATE AT LAST REVIEW	80
TABLE	X HIV CLINICAL STAGE AT FIRST CONTACT	82
TABLE	XI CHANGES IN HIV CLINICAL STAGE DURING FOLLOW-UP	87
TABLE	XII DYSENTERY AND ARTHRITIS ADMISSIONS 1985-1994 AS PER CENTAGE OF YEARLY ADMISSIONS	97
TABLE	XIII SULPHASALAZINE THERAPY: CLINICAL RESULTS	99
TABLE	XIV SULPHASALAZINE THERAPY: LABORATORY RESULTS	100

FIGURE 1:	AGE SPECTRUM OF PATIENTS WITH SERONEGATIVE ARTHRITIS	39
2:	HIV-SEROPREVALENCE BY AGE AND BY DIAGNOSTIC SYNDROME	61

LIST OF ABBREVIATIONS AND DEFINITIONS

1: RELATING TO DIAGNOSIS

AA	"Arthritis Alone" Refers to a group of patients with non-specific arthritis without associated extra-articular features.
AS	Ankylosing Spondylitis
JCA	Juvenile Chronic Arthritis
RA	Rheumatoid Arthritis
REA	Reactive Arthritis
RSA	Reiter's Syndrome/Disease
PSA	Psoriatic Arthritis
S.L.E.	Systemic Lupus Erythematosus
USA	Undifferentiated Spondyloarthropathy

2: RELATING TO HIV INFECTION:

HIV	Human Immunodeficiency Virus
PGL	Persistent Generalised Lymphadenopathy

3: RELATING TO JOINTS:

A-C-J	Acromio-Clavicular Joint
DIP	Distal Interphalangeal Joint
MCP	Metacarpo-phalangeal Joint
MTP	Metatarso-phalangeal Joint
PIP	Proximal Interphalangeal Joint
S-C-J	Sterno-Clavicular Joint
SIJ	Sacro-iliac Joint
TMJ	Temporo-mandibular Joint

ENTHESITIS:

- 4: The entheses are the points of insertion of tendos and ligaments into bone. Enthesitis refers to inflammation of these structures.
- 5: SERONEGATIVE ARTHRITIS: Seronegative spondyloarthropathies are also refered to as seronegative arthritides. The terms seronegative arthritis and spondyloathropathies are used interchangeably in this thesis.
- 6: SERONEGATIVE SPONDYLOARTHROPATHIES: These are a group of disorders which are linked by their strong association with HLA Antigen B27, negative tests for Rheumatoid factors (hence the name seronegative Arthritis or Seronegative Spondyloarthropathies) and shared clinical features such as spine, sacroiliac joint and skin involvement.

SUMMARY

BACKGROUND:

A growing body of data has established that most rheumatic diseases are prevalent in the populations of sub-Saharan Africa. However, the spectrum and relative frequencies of these disorders remain unknown in many parts of the continent. The AIDS epidemic has brought, in its wake, an unprecedented increase in a variety of rheumatic and other autoimmune diseases. Many of these HIV associated syndromes have also been described in African patients. The extent to which the nosology of Rheumatic disorders has been affected by the AIDS epidemic has not been investigated before.

DESIGN AND METHODS

The clinical Syndromes of 510 consecutive patients (326 males and 184 females) seen at an arthritis clinic between January, 1994 and December, 1995 were characterised. A prospective as well as retrospective evaluation of patients with seronegative (i.e. Rheumatoid factor negative) arthritis was conducted in order to establish the natural history of HIV-associated arthritis. HIV-positive patients with polyarticular disease resistant to non-steroidal anti-inflammatory drugs were entered into an open study to establish the safety and efficacy of sullphasalazine.

RESULTS

An inflammatory arthritis was the most common (365 of 510, 72 percent). The clinical syndromes included Ankylosing spondylitis (AS: n=01); Psoriatic Arthritis (PSA: n=11); undifferentiated spondyloarthropathy (USA: n=112); Reactive arthritis (REA: n=119) and Arthritis Alone (AA: n=122). Three hundred and two (82% of 365) of this subgroup of patients were tested for HIV and 253 (84 percent) were sero-positive.

The only AS patient was HIV-seronegative. Of the remainder, the HIV seroprevalence was highest in the USA group (98% of 100 patients tested) and lowest in the AA group (65% of 91 tested). In the ReA group 86 of 99 (87%) tested seropositive. Ten (91%) of the 11 PsA patients tested seropositive.

Enthesitis was common in this group of patients and occurred in 51% (185 of 365) of them. The lesion was strongly associated with HIV infection (156 of 165 or 95% tested seropositive). In addition, an enthesitis was the only lesion in a further ten patients and 100% of eight tested HIV - seropositive.

There was a 100% HIV seroprevalence among women with Reactive arthritis and undifferentiated spondyloarthropathy that were tested (29 and 37, respectively).

Dactylitis occurred in 31 patients (8.5% of 365) and 97% of 30 patients tested HIV -seropositive. Eleven patients had anterior uveitis. Ten of 10 patients with uveitis and 7 of seven with erythema Nodosum were HIV-seropositive.

The disease in HIV-positive patients differed from that in HIV-negative patients by tending to be polyarticular (mean joint count 10 versus 4, respectively) and by tending to be more chronic with frequent relapses and exacerbations (mean duration 18 months in HIV-positive compared to 9 months in HIV-negative patients).

Other conditions were myositis-Myopathy (n=24: 74% of 23 HIV-positive); Rheumatoid arthritis (n=21: none of 13 tested HIV positive); Gout (n=14); Osteoarthritis (n=09: none of 7 tested HIV positive); Soft tissue lesion (n=08: 17% of 06 tested HIV-positive). Septic arthritis (n=5: 02 of 02 tested HIV-positive); Palindromic Rheumatism (n=5: none of 4 tested HIV-positive); Polyarthralgia (n=5: 4 of 4 tested seropositive); Neisserial reactive arthritis (n=4: all were HIV positive).

In the miscellaneous category there were osteoporosis (n=3); Bone tumour (n=3); SLE (n=2) Rheumatic Fever (n=2); Avascular necrosis (n=2), Herpes zoster arthritis (n=2); Disc Prolapse (n=2) and sickle cell arthritis (n=1).

CONCLUSION:

This study has defined the relative frequency of rheumatic diseases in patients attending this hospital in Lusaka. Since the U.T.H. largely functions as a primary care facility rather than its intended role of a tertiary referral hospital, this spectrum of diseases may well be representative of the true picture for Lusaka.

The influence of HIV on the spectrum of Rheumatic disorders at this institution is striking. This data provides additional evidence for an association between HIV infection and the occurrence of spondyloarthropathies in indigenous black Africans.

INTRODUCTION AND REVIEW OF LITERATURE

A wide spectrum of Rheumatic Syndromes are recognised to occur in association with HIV infection. These include inflammatory joint disease, first reported by Winchester et al (1) and, subsequently by other groups of workers (2-5); polymyositis (6-9); Vasculitis (10,11); the sicca syndrome (12-14); psoriatic arthritis (15, 16 17); and various Autoimmune phenomena (18, 19). The subject has been reviewed by Kaye (20), Solomon et al (21) and by Golbus (22). The nosology of Rheumatic diseases and the influence of Human Immunodeficiency virus (HIV) infection on the prevalent types remains unknown in most parts of sub-Saharan Africa.

PREVALENCE

It is recognised that rheumatologic lesions may be the first manifestation of HIV infection in some patients. However, the region to region variation in the prevalence of HIV- associated rheumatic syndromes is very wide. This has varied from 4 percent in the North West Thames of London (23) to as high as 71 percent of patients attending an immunodeficiency clinic in Florida (3). The variation in prevalence may reflect differing methods of patient recruitment, but local sociodemographic factors may be equally important in determining prevalence of Rheumatic diseases.

AETIOLOGIC ROLE OF HIV

In this regard, the observations of Clark et al (24), Solinger and Hess (25) and Hochberg et al (26) warrant particular note. An association between HIV infection and Reiter's Syndrome past or present was not demonstrated by these studies.

Hochberg et al (26) determined the prevalence and incidence of Reiter's Syndrome in 1133 homosexual/bisexual men enrolled in a multicentre AIDS Cohort study in Baltimore, USA. They found no difference in the prevalence of Reiter's Syndrome at entry into the study in 1984 between 357 HIV-positive and 776 HIV-negative men: five per 1000 in both groups. During a follow-up period of five years, one case of Reiter's Syndrome developed among each group of HIV-positive and HIV-negative men.

In a similar study, Clark et al (24) found no association between HIV infection and a history of Reiter's Syndrome at entry into a Cohort study of 1043 predominantly homosexual men. They analyzed data from the San Francisco Men's Health study and found that only two (0.5% of 403 HIV-positive and two (0.3%) of 615 HIV-negative men had a history of Reiter's Syndrome at entry.

Solinger and Hess (25) obtained similar results, finding only one case of Reiter's Syndrome among the first 1000 HIV-positive subjects evaluated in the AIDS clinic and Treatment centre at the University of Cincinnati.

ROLE OF ADDITIONAL FACTORS

While these data fail to demonstrate an association between HIV infection and the occurrence of Reiter's Syndrome in homosexual/bisexual men, it is quite conceivable that the concurrence of Reiter's Syndrome and HIV infection reported by others may be a result of an indirect effect occasioned by an increase in the prevalence of infection by arthritogenic organisms amongst HIV infected persons. This hypothesis is supported by data from Clark et al's study (24) which identified an association between diarrhoeal illness and occurrence of Reiter's Syndrome among the HIV positive subjects. Furthermore the use of pharmacologic agents to delay the development of immunodeficiency which is wide spread in America and other Western Nations may alter the occurrence of Reiter's Syndrome and, indeed, the occurrence of other Rheumatic diseases in susceptible HIV infected individuals. Lastly, it is also conceivable that reduction in high risk sexual behaviour by reducing the occurrence of arthritogenic infections, may alter the natural history of Reiter's syndrome. This has been documented with respect to the occurrence of Kaposi's Sarcoma (27).

It is likely that many questions will remain unanswered for a long time regarding the link between HIV infection and joint disease. Difficulty of finding suitably matched HIV-negative controls is a major constraint. Additionally, difficulties with nomenclature and classification of rheumatic disease in the context of HIV infection are also encountered.

THE SITUATION IN AFRICA:

In Africa, such problems are compounded by other factors such as inadequate training in clinical Rheumatology, limited or non-existent investigative facilities and the high patient drop-out rate in long-term follow-up.

PREVALENCE AND THE ROLE OF HLA

There is no information on the prevalence of HIV-associated rheumatic disease in Africa. However, Hospital-based Surveys report an increase in the prevalence of Reactive arthritis and an association between this syndrome and HIV infection (28-30). Furthermore, no association with HLA-B27 has been demonstrated in African patients with HIV associated Reactive Arthritis (28). This is in contrast to the disease in caucasians where the frequency of HLA-B27 has varied between 71 and 79 percent (21,31) proportions which do not differ significantly from those obtained in patients with non HIV-associated Reactive arthritis.

POSSIBLE PATHOGENIC MECHANISMS:

Reports of increased prevalence of Reactive arthritis in Africa come as something of a surprise because the prevalence of this disease and that of seronegative spondyloarthropathies in general has hitherto been rare. This rarity has been attributed to the low prevalence of HLA - B27 in the black race (32). The prevalence of HLA - B27 in the Black population in Central and South Africa appears to be less than 1% (33). The lack of association with HLA - B27 raises further questions regarding pathogenetic mechanisms for Reiter's Syndrome and reactive arthritis in Africa. Although observations from North America seem to negate a direct aetiological role for HIV the possibility still exists that arthritis may be caused by specific antigenic strains of the HIV virus or a constellation of such strains in a particular individual. However, on the basis of available information, it seems more plausible to assume that the immunological disturbance created by HIV infection sets the background against which an aberrant immune response occurs, resulting in the Reiter Syndrome and Reactive arthritis following infection with arthritogenic organisms (1).

ROLE OF INFECTION:

It is probable that the African environment predisposes HIV infected patients to an increased risk of infection with arthritogenic organisms since gastrointestinal and sexually acquired infections may occur far more frequently in Africa than in industrialised nations due to overcrowded and insanitary living conditions in the former. It is possible that this might account, at least in part, for the observed increase in the incidence of reactive arthritis. However, attempts to identify precipitating gastrointestinal or genitourinary pathogens have been unsuccessful so far, in Africa (28, 30). In contrast, approximately one third of patients of HIV-associated Reactive arthritis from Western nations have had a documented infection with a known arthritogenic enteric pathogen including shigella flexneri, Salmonella, campylobacter jejuni, and Yersinia enterocolitica and pseudotuberculosis. In about another third infections not traditionally associated with Reactive arthritis have been temporarily associated with the onset of arthritis. In this regard, mycobacterium avium intracellulare is the most prominent (21). Technical difficulties certainly preclude a thorough search for trigger infections in Africa, but clinical observations seem to indicate that even during an epidemic of shigella dysentery, HIV infected patients with Reactive arthritis are less likely to report a preceding episode of dysentery than HIV negative patients

with Reactive arthritis. Kasongo (1993) studied 119 patients with Reactive arthritis between March, 1991 and September, 1992 at the height of a shigella dysentery epidemic in Lusaka. HIV negative patients reported a history of preceding dysentery more frequently than the HIV positive patients in his series (33 versus 23 percent) (30). It may be that HIV-positive people suffer from non-bloody /shigella dysentery more often than HIV-negative ones. However, a study from a rural area of Zambia suggests that in an epidemic of dysentery, HIV-positive individuals are more likely to suffer clinical disease (34). In this study an HIV seroprevalence rate of 62 percent was found among 200 dysentery patients seen during an epidemic of the disease. The HIV seroprevalence rate was 15 percent in a control population of patients with acute malaria and injuries seen at the same hospital during the 3 months study period. The study does not mention the existence of arthritis in this series of patients, but obviously raises further issues regarding the role of Shigella enteritis as a trigger factor in HIV-associated reactive arthritis. Some light may be shed on the subject by a retrospective review of the incidence and prevalence of dysentery and arthritis over the past couple of years.

CASE DEFINITION

The issue of case definition deserves special consideration in Africa. Lack of diagnostic tests for reactive arthritis make it difficult to estimate the prevalence of the condition in any community. In Africa, the situation is exacerbated by the absence of specialist rheumatologists and limited laboratory facilities for investigation of patients with arthritis. As a result, clinical recognition of the disease may be difficult and, without laboratory support, exclusion of other causes of arthritis may be impossible. There is, therefore, an omnipresent danger of assigning a wrong diagnostic label to arthritic conditions in Africa.

Great lessons are being learnt from careful evaluation of patients with a type of polyarthritis thought to be peculiar to the Tropics. This entity, designated "TROPICAL POLYARTHRITIS", has been described from many parts of the Tropics (35-41). However, the implication that this is a distinct entity has been challenged (42) and, where such patients have been fully investigated, it has often been possible to revise the diagnosis to one or the other of the specific Rheumatologic disorders (43, 44).

It is possible that thorough investigation of patients with HIV-associated Reactive arthritis may reveal them to be a heterogenous group who only have the presence of HIV infection in common. Owing to the lack of association with HLA-B27 and to the fact that initial cases reported out of Africa exhibited a comparatively milder non-erosive disease without enthesopathy which responded well to non-steroidal antiinflammatory drugs(28), workers from elsewhere have pointed out that this finding is more consistent with a virally-induced arthropathy rather than a true reactive arthritis (23).

A number of virus infections are commonly accompanied by short-lived oligo- or polyarticular arthritis. Among the most clinically important viral infections associated with arthritis are rubella, parvovirus, alphaviruses and hepatitis A and B (45). The presence of characteristic clinical features of these infections usually makes the diagnosis easy, but a high index of suspicion is required for the diagnosis to be considered. What role other viral infections play in the causation of HIV-associated arthritis will remain unidentified for long owing to limited laboratory facilities referred to above.

The clinical recognition of reactive arthritis in Africa must, therefore, depend heavily on the identification of extra articular features of the disease such as the presence of preceding infection, enthesopathic lesions, sacroiliitis or mucocutaneous lesions.

TREATMENT ISSUES:

Treatment of Rheumatic disorders in HIV-infected individuals has proved especially difficult and presents many challenges to the clinician (2,21). Response to non-steroidal antiinflammatory agents is generally poor. Available data indicate that the use of corticosteroids and disease modifying antirheumatic drugs may increase the risk of progression to AIDS, and death (2,21). These observations add to the clinical dilemma and make the handling of patients with HIV-associated conditions particularly difficult as they often have unusually severe, sustained and progressive disease.

Chloroquine and non-steroidal antiinflammatory drugs have been used with some benefit in Zimbabwean patients (28), but in Kasong's series (1993), HIV-positive patients responded less well to Indometacin than HIV-negative patients; only 4% of HIV-positive patients returned to normal at 6 months compared with 23% of the HIV-negative patients (30).

The use of intra-articular depot steroid injections (21) and of sulphasalazine have produced encouraging results in the treatment of HIV-associated arthritis, in the West (46) and in Togo, West Africa (47). However, large studies are required to assess the usefulness and safety of these and other antirheumatic drugs and to establish cheap effective remedies.

THE HIV THREAT: IMPLICATIONS FOR AFRICA

During the past decade, HIV/AIDS has become established as a major health problem. According to recent estimates, up to 17 million people worldwide may be infected with the Human Immunodeficiency virus. Over 80 percent of these HIV victims are in the developing countries - countries which, owing to their financial situation, are less able to cope with the AIDS problem in general and with specific issues raised by the AIDS epidemic in particular.

The outlook remains bleak for the developing world. In spite of unrelenting public effort to stem further transmission and spread of HIV infection, there is no indication of any gains in this campaign. What is more, the epidemic is just now moving into the early explosive phase in many places, such as in Asia.

What all this adds to is the fact that HIV-associated disorders will continue to dominate the practice of Medicine in much of the Third World and in Sub-Saharan African in particular. At our current level of knowledge of such disorders in African HIV-infected patients, we are obviously ill-equipped to provide ideal care for such patients. The need for research cannot be over-emphasised.

THE GREY AREAS

As regards the problem of HIV-associated arthritis several issues remain to be elucidated. There is an urgent need to throw some light on several gray areas on the subject, chief amongst which are the following:

1. What role genetic factors play in the pathogenesis of the disease in Africa. The status of HLA-B27 needs evaluating further in larger studies. The possibility that an as yet unidentified subtype of HLA-B27 might be responsible exists. In this regard, recent studies in Gambia using newer techniques with polymerase chain reaction (PCR) have found that nearly 3% of the population carry HLA-B27 but that they carry a subtype (HLA-B2703) which is not disease-associated thus accounting for the low prevalence of reactive arthritis amongst this population (48). Finally, the role of HLA antigens known to cross react with HLA-B27 (the B7-cross Reactive Group (B7-CREG) demands attention.

These antigens probably have a role to play in HLA-B27 negative spondyloarthropathies (49). Stein et al found B7-CREG antigen in 7 of 10 Zimbabwean patients with Reiter's Syndrome and in one of 9 patients with Ankylosing spondylitis (50).

2. What role known arthritogenic enteric and genito-urinary infections play in the causation of the disease.
3. What role other viral and parasitic infections play. In particular, the influence of other Human retroviruses such as HTLV-I needs investigating. This retrovirus is known to cause a variety of Rheumatic conditions in man including arthritis (51, 52). Furthermore, HTLV I and II share the same epidemiologic risk factors as HIV and are endemic in many parts of Africa.
4. The course and natural history of the disease has not been adequately studied. The influence of Arthritis on the clinical behaviour of HIV infection needs evaluating in African patients who in most instances receive less than ideal treatment for their arthritis and who have no access to AZT and other therapies known to delay the progression of HIV infection.

5. The magnitude of the health problem presented by rheumatologic manifestations of HIV infection in general and the health problems presented by inflammatory Arthritis in particular remains unaddressed. The psychological and sociological impact of a persistent painful condition constantly (day and night) gnawing away at a body and a conscience already burdened by other diseases and by the knowledge that in the background of all this there is an incurable disease, must be great.
6. Finally, specific questions raised by previous observations in Zambia need answers. Firstly, one may pose the question: "Has the incidence of Reactive Arthritis really risen in Lusaka, Zambia?" Although the fact that the prevalence of arthritis problems has risen amongst Hospital patients is not at issue, available reports on the subject (29,30) do not answer the question fully. What we are seeing may merely be one or the other of the many types of arthritic syndromes described in HIV-infected patients elsewhere (21) and not reactive arthritis. Documentation of the presence of extra-articular lesions peculiar to reactive arthritis will provide additional evidence of the presence of an increased prevalence of the condition. Although such lesions may have been looked for in previous studies, they are not mentioned in the reports.

Secondly, if Reactive Arthritis is indeed on the increase here, is it really associated with HIV-infection? Or is the observed rise in the incidence of the disease due to an independent set of epidemiologic factors that have become prevalent for the first time coincidentally with the HIV epidemic? In this regard the Shigella and meningococcal epidemics that have hit Zambia in recent years deserve consideration. Both infections may be associated with arthritis. Kasongo (30) concluded that a finding of a seroprevalence rate of 55 percent among his 119 patients with reactive arthritis constituted a strong association between this condition and HIV infection. Closer scrutiny of the situation, however, suggests that his conclusion may be erroneous. In assigning statistical significance to his findings, he took as his reference population the general Lusaka population amongst whom the HIV seroprevalence rate is generally viewed to be between 30 and 35 percent. The seroprevalence rate among hospital patients must, obviously, be much higher. In a survey to assess the HIV infection load on the Internal Medicine service at the U.T.H. in the latter part of 1992, a seroprevalence rate of 70 percent was found among in-patients. It is likely that the HIV seroprevalence rate among the general population of patients coming to the U.T.H. with medical

conditions (of which reactive arthritis is one) may be around 50 percent. If one drew a random sample of 119 individuals from such a universe of patients it would be possible to find by chance alone a seroprevalence rate of from 41 to 59 percent ($50 \pm 2SE$, 95% confidence interval). The finding of a 55% seroprevalence rate by Kasongo, therefore, does not reach statistical significance when such a universe of patients is assumed. It is likely that Kasongo's finding was an epiphenomenon, reflecting the HIV seroprevalence rate in the general population of adult hospital patients. This fact taken together with the lack of a demonstrable difference in the clinical behaviour of the disease in HIV-positive and HIV-negative patients, except the suggestion that the former group of patients might respond less well to non-steroidal antiinflammatories, strengthens the view that the current increase in the prevalence of Arthritic problems may be occurring independently of the HIV epidemic.

Finally, one needs to answer the question: "To what extent do other features of HIV infection affect response to therapy for arthritis". This question needs addressing since some patients who develop reactive arthritis may already be burdened by other features of HIV infection so that they may not tolerate medicines for arthritis as well as HIV negative patients. Furthermore, within the HIV

infected group of patients, it is essential to stratify therapeutic response according to the stage of the HIV infection.

A preliminary analysis of the first 160 consecutive patients seen between January, 1994 and January, 1995 (mainly from Arthritis clinic) reveals that 113 of them had seronegative arthritis. Of these 113 patients, 55 (49%) had an HIV result and, of these 45 (82%) were HIV seropositive.

Enthesopathic lesions were very common, occurring in 71 of the 113 patients (63%). There was a suggestion that enthesopathy may be a marker of HIV infection, occurring in 34 (76%) of the 45 HIV positive patients and in 4 of the 10 HIV negative patients. We resolved to investigate this relationship further.

OBJECTIVES OF THE STUDY

1. To assess the frequency and spectrum of seronegative arthropathies occurring in the context of HIV infection in adult Zambians and to test the hypothesis that reactive arthritis is the predominant HIV-associated arthropathy in Lusaka.
2. To ascertain and document the occurrence of enthesitis and other extra-articular lesions in Zambian patients with seronegative arthritis.
3. To assess the course and natural history of HIV-associated arthritis in indigenous Black Zambians.

4. To assess the safety and efficacy of Sulphasalazine in the treatment of HIV-associated arthritis.
5. To assess the influence of the Shigella dysentery epidemic on the prevalence of non-septic arthritis at the U.T.H., Lusaka.

PATIENTS AND METHODS

PATIENTS AND METHODS

Patients attending an arthritis clinic with non infective rheumatic disorders between January 1994 and december, 1995 were studied prospectively. Patients were referred to this clinic from the hospital's main Filter Clinic, Casualty Department and from Surgical and Medical in-patient and out-patient services. A few patients were referred from the Paediatric and Obstetric services in the hospital.

All patients were assessed by the author and were questioned in detail about their joint symptoms, heel pain, back pain or stiffness, mucosal and skin lesions, symptoms of acute anterioruveits,conjunctivitis,urethritis, diarrhoea and venereal exposure. Their past and family histories of arthritis were recorded and where possible, the affected family member was persuaded to attend for examination.

Demographic data (age, sex, duration of disease) were obtained for all patients. A retrospective evaluation was conducted in all patients with a past history of arthritis. This consisted of details of the previous attack(s) including the joints or joint areas affected, the duration of the attacks and accompanying extra-articular features if these could be recalled.

A thorough physical examination was conducted with special attention to the joints and entheses, spine, skin, eye, buccal mucosa and genitalia. All the tender and swollen joints were recorded individually in a joint count chart as were the enthesopathies.

The entheses examined routinely were: the nuchal crests, cervical spinous processes, the costochondral joints, the medial and lateral epicondyles of the humerus, the tibial tuberosities, the medial and lateral condyles of the femur and tibia, the head of the fibula, the calcaneal insertions of the plantar fascia and the Achilles tendon, the sacroiliac joints and the medial and lateral malleoli.

Blood samples were obtained for Biochemical.

Haematological and Serological tests for Rheumatoid factor (latex fixation test) and for antibodies to HIV by enzyme-linked immunosorbent assay, Elisa (Wellcozyme HIV recombinant, VK56/57, Murex Diagnostics, Dartford, UK) and a particle agglutination test (serodia HIV, Fujirebio, Tokyo, Japan).

HAEMATOLOGICAL TESTS

The Full Blood Count (FBC) was checked using the coulter counter method (Coulter electronics Ltd. England). The erythrocyte sedimentation rate (ESR) was measured using the westergren method. These tests were repeated at monthly intervals for patients receiving sulphasalazine and at six to 12 weekly intervals for other patients unless the clinical state demanded more frequent testing.

BIOCHEMICAL TESTS

Renal and Hepatic function were tested using an autoanalyser (COBAS MIRA). These tests were repeated at six to 12 weekly intervals.

OTHER TESTS

Standard radiographs were performed as indicated clinically. Routine bacteriological procedures were used for stool and synovial fluid culture. The concentration and modified Ziehl-Neelsen methods were used for the detection of stool protozoa.

FOLLOW UP

During the first six months of the study patients were reviewed fortnightly for the first six weeks and once monthly thereafter. As the clinic grew larger and as we became more familiar with the behaviour of the disease in HIV infected patients, the review protocol was modified and patients were seen once every one to two months.

DRUG THERAPY

Indomethacin was the first line non-steroidal antiinflammatory drug. Patients received a daily dose of 75mg or 150mg in three divided doses depending on disease severity adjusting upwards to a maximum daily dose of 200mg if the starting dose was not completely effective.

DEFINITIONS

1 REACTIVE ARTHRITIS (ReA)

Arthropathies that were designated as reactive arthritis included:-

- (a) Reiter's Syndrome (Full triad or incomplete)
- (b) Arthritis following sexually acquired or enteric infection.

2. REITER'S SYNDROME/DISEASE (RS)

Reiter's Disease was diagnosed in individuals who satisfied the criteria proposed by Calin (53) with one exception; those with a history of dysentery were not necessarily classified as Reiter's disease unless another defining feature was present. The designation Incomplete Reiter's Disease was applied to those NOT possessing the full triad of Arthritis, urethritis and Conjunctivitis.

3. PSORIATIC ARTHRITIS (PsA)

Psoriatic Arthritis was diagnosed in patients satisfying the criteria proposed by Vasey and Espinoza (54).

4. UNDIFFERENTIATED SPONDYLOARTHRITIS (USA)

USA was diagnosed in individuals presenting with arthritis in association with one or more of the following:

Dactylitis, Tendonitis, Enthesopathy and/or painful heels.

5. ARTHRITIS ALONE OR NON-SPECIFIC ARTHRITIS (AA)

AA was diagnosed in those patients with acute arthritis who did not fulfil the criteria of a recognised Rheumatic disorder.

6. ANKYLOSING SPONDYLITIS (AS)

AS was diagnosed in patients satisfying the modified New York criteria (55).

7. HIV CLINICAL STAGE

The clinical stage of HIV infection was made according to World Health Organisation (WHO) classification (56).

Stage 1: Asymptomatic infection, persistent
Generalised lymphadenopathy (PGL).

Stage 2: Weight loss (less than 10%), Herpes
Zoster.

Stage 3: Weight loss (greater than 10%),
persistent diarrhoea, oral
candidiasis, pulmonary tuberculosis.

Stage 4: HIV-wasting syndrome, AIDS-defining malignant or infectious disease.

8. THERAPEUTIC RESPONSE

The therapeutic response was evaluated at every visit. The therapeutic state at the last contact was graded on the basis of a modification of the American Rheumatism Association (ARA) criteria (57):

- . Grade I (COMPLETE REMISSION): Disappearance of systemic signs as well as signs of joint inflammation and extra-articular activity.
- . Grade II and III (IMPROVED): Reduction in tender or swollen joints and extra-articular activity. No new sites involved.
- . Grade IV (UNIMPROVED): Undiminished systemic signs. Signs of joint inflammation and of extra-articular activity remain the same or new sites involved or there is an exacerbation.

9. FUNCTIONAL CAPACITY

Functional capacity was defined by a modification of the ARA grading system (57):

- CLASS I: NORMAL FUNCTION - complete ability to carry on all usual duties without difficulty.
- CLASS II: NORMAL FUNCTION ALTHOUGH with PAIN AND DIFFICULTY or Limitation of motion at one or more joints.
- CLASS IIIa: LIMITED FUNCTION - Ability to do paid work or house work diminished but self-sufficient in activities relating to personal hygiene and care.
- CLASS IIIb: Limited Function as for IIIa but not self-sufficient.
- CLASS IV: INCAPACITATED - Chairbound or bedridden with little or no self care.

10. SAMPLE SIZE

Based on a prevalence of Enthesitis of 63% among the first 113 patients with seronegative arthritis we determined to recruit 360 patients with seronegative arthritis. This sample size would enable us estimate the true prevalence of enthesopathies in this population of patients with a statistical power of 80 per cent.

All the patients with other conditions seen during this time were studied for comparison of relative frequencies and spectrum of prevalent rheumatic disorders.

11. SALPHASALAZINE TRIAL

HIV positive patients with seronegative arthritis who failed to register adequate improvement on maximal doses of Indomethacin after at least eight weeks of treatment were entered into an open study of sulphasalazine to establish efficacy and safety.

Additional entry criteria were (Polyarticular disease (at least 6 joints involved); white Blood Cell count (WBC) $\geq 4 \times 10^3/\text{mm}^3$; Haemoglobin $\geq 9\text{g/dl}$; Platelet count $\geq 150,000/\text{mm}^3$).

Efficacy measures included pain score (visual analogue scale); Tender and swollen joint count (modified 28 joint count using the MTP and TOE PIP joints in place of the MCP and Finger PIP Joints and the Ankle Joints in place of the Shoulder Joints); Global Assessment by patient (visual analogue scale) and by observer (5 point score) at monthly intervals.

FBC, ESR, Hepatic and Renal function were also assessed at monthly intervals.

12. APPROVAL

Permission for the study was granted by the Hospital Ethics Committee and by the Research Ethics committee of the University of Zambia.

RESULTS

During the 24 months period 510 patients were studied.

AGE AND SEX:

There were fifteen children (11 male and 4 female) below the age of 15 years. Of the remaining 495 adults, there were 315 males and 180 females.

RACE:

All except eight adult patients were indigenous black Africans. Of the eight non-black patients, four were Indians (1 male: Gout, 1 female: Rheumatoid Arthritis, 1 male and 1 female: Palindromic Rheumatism). The other four were Afro-Caucasian Coloureds (1 male: Gout, 1 male: Osteoporosis, 1 male and 1 female: Undifferentiated Spondyloarthritis).

CLINICAL SYNDROMES:

The diagnoses and clinical features of these patients are shown in Table 1. The largest group fell in the SERONEGATIVE ARTHRITIS diagnostic category.

HIV INFECTION:

Four hundred and three (81 percent) of the 495 adults were tested for Human Immunodeficiency Virus (HIV) and 303 (75 per cent) were seropositive.

SOURCE:

Ninty-two patients (18 percent) of the 510 were seen as In-patients. The rest were seen as out-patients and 3 percent of them came as direct referrals from General Practitioner Colleagues. However, other patients referred to the U.F.H. by general practitioners reached the clinic via Casualty or Filter clinic.

TABLE I: DIAGNOSTIC CATEGORIES

DIAGNOSTIC GROUP	NO. OF PATIENTS (% OF 510)	M : F	MEAN AGE (YR) (RANGE)	HIV POSITIVE PROPORTION
SERONEGATIVE ARTHRITIS	365(72%)	240 : 125	33.1 (15 - 77)	84% (253/302)
MYOSITIS/MYOPATHY	24(4.7%)	20 : 04	36.0 (21 - 55)	74% (17/23)
RHEUMATOID ARTHRITIS	21(4.1%)	04 : 17	51.1 (17 - 80)	00 OF 13
GOUT	21 (4.1%)	19 : 02	53.7 (22 - 78)	23% (3 OF 13)
JUVENILE Chronic ARTHRITIS (2 > 15 YR OLD)	14 (2.8%)	11 : 03	10.9 (4.5 -22)	00 OF 01
ENTHESITIS ALONE	10 (2.0%)	05 : 05	32.6 (23 -54)	100% (8 OF 8)
OSTEOARTHRITIS	09 (1.8%)	03 : 06	59.1 (50-70)	00 OF 07
SOFT TISSUE LESION	08 (1.5%)	02 : 06	42.1 (25 - 70)	17% (01 OF 06)
SEPTIC ARTHRITIS (2 CHILDREN)	05 (1.0%)	02 : 03	20.6 (5 - 37)	2 OF 2 ADULTS
PALINDROMIC RHEUMATISM	05 (1.0%)	01 : 04	46.8 (33-75)	00 OF 04
POLYATHRALGIA	05 (1.0%)	05 : 00	37.2 (22 - 54)	4 OF 4
NEISSERIAL REACTIVE ARTHRITIS	04 (0.8%)	02 : 02	25.8(23-30)	4 OF 4
MISCELLANEOUS (1 CHILD)	19 (3.7%)	12 : 07	36.6 (11-82)	44% (07 OF 16)
TOTAL	510(100%)	326:184 (2 : 1)	37.4 (4½ - 82)	75% (303 OF 403)

RESIDENCE:

Sixty-one percent of these patients came from the city's high density/shanty compounds. Thirty percent were from medium density residential areas and 9 percent were from low density residential areas.

DATA PRESENTATION:

The results will be presented in two parts. Part 1 describes the features of patients with seronegative arthritis and those with enthesitis alone. Part 2 looks at patients with the other conditions.

FORMAT:

For the seronegative arthritis group, an overview covering all patients studied will be given first. Then, the HIV-seropositive and negative populations shall be compared and contrasted. Thereafter, comparisons shall be made among HIV-seropositive patients with different diagnostic syndromes.

This general format shall be followed whenever appropriate in dealing with conditions in part 2 of the report.

PART I: SERONEGATIVE ARTHRITIS AND "ENTHESITIS ALONE"

Three-hundred and sixty-five patients (72 percent) of 510 had seronegative arthritis. Ten patients had isolated enthesitis (the "ENTHESITIS ALONE" group).

Of the 365 patients with seronegative arthritis, 243 (67 percent) satisfied the European spondylarthropathy Study Group (ESSG) criteria for diagnosis of spondylarthropathy (58).

All patients had synovitis. The additional variable was ENTHESITIS in 135 patients, preceding Urethritis or Cervicitis or Dysentery in 96 patients, Psoriasis in 11 patients and Radiological sacroiliitis in the patient with Ankylosing spondylitis (AS).

A: THE "ENTHESITIS ALONE GROUP"

In Ten patients (5 male and 5 female) enthesitis was present as an isolated feature. There was no history of previous arthritis in any of the patients. However, there is evidence that some of these patients may eventually develop arthritis. This was observed in 4 additional patients who were thus reclassified under the Undifferentiated spondylarthropathy group.

The lesions observed were clinical sacroiliitis in five patients (3 male and 2 females). All five patients had unilateral involvement but the symptomatic side alternated between the two sides in the course of follow up in three patients. Three patients (1 male and 2 females) had painful and tender heels. This was unilateral in one of the two females. Two patients (1 male and 1 female) had polyarthralgia around the ankle and knee joints. The male patient also had Periostitis of the lower thirds of the tibiae and fibulae.

Additional findings in other patients of this group were pain and tenderness at the femoral greater trochanters in the female patients with sacroiliitis; Urethritis and bilateral conjunctivitis preceded by Shigella dysentery in the male patient with heel pain and tenderness; chronic passage of small quantities of stools, mixed with some blood and mucus in the female patient with polyarthralgia and in one of the male patients with sacroiliitis.

All patients had had nearly persisted disease from onset. The mean duration of disease was 4.4 months (Range 1 week to 1 year).

Eight patients (5 male and 3 females) were tested for HIV and all were seropositive.

There was favourable response to Non-steroidal anti-inflammatory drugs (NSAID) in Eight patients. In two patients (1 male with polyenthesitis and 1 female with heel pain). Symptoms were sustained and required repeated local steroid injections to control.

B: THE SERONEGATIVE ARTHRITIS GROUP: OVERVIEW

B1: SYNDROMES:

There were 11 patients with Psoriatic arthritis (PsA); 112 had undifferentiated spondyloarthritis (USA); 119 had Reactive arthritis (ReA); and 122 had arthritis without associated extra-articular lesions ("ARTHRITIS ALONE", AA GROUP). Forty-eight of the patients with Reactive arthritis satisfied Calin's criteria for the diagnosis of Reiter's syndrome (RS) (53).

These diagnostic syndromes are shown in Table II.

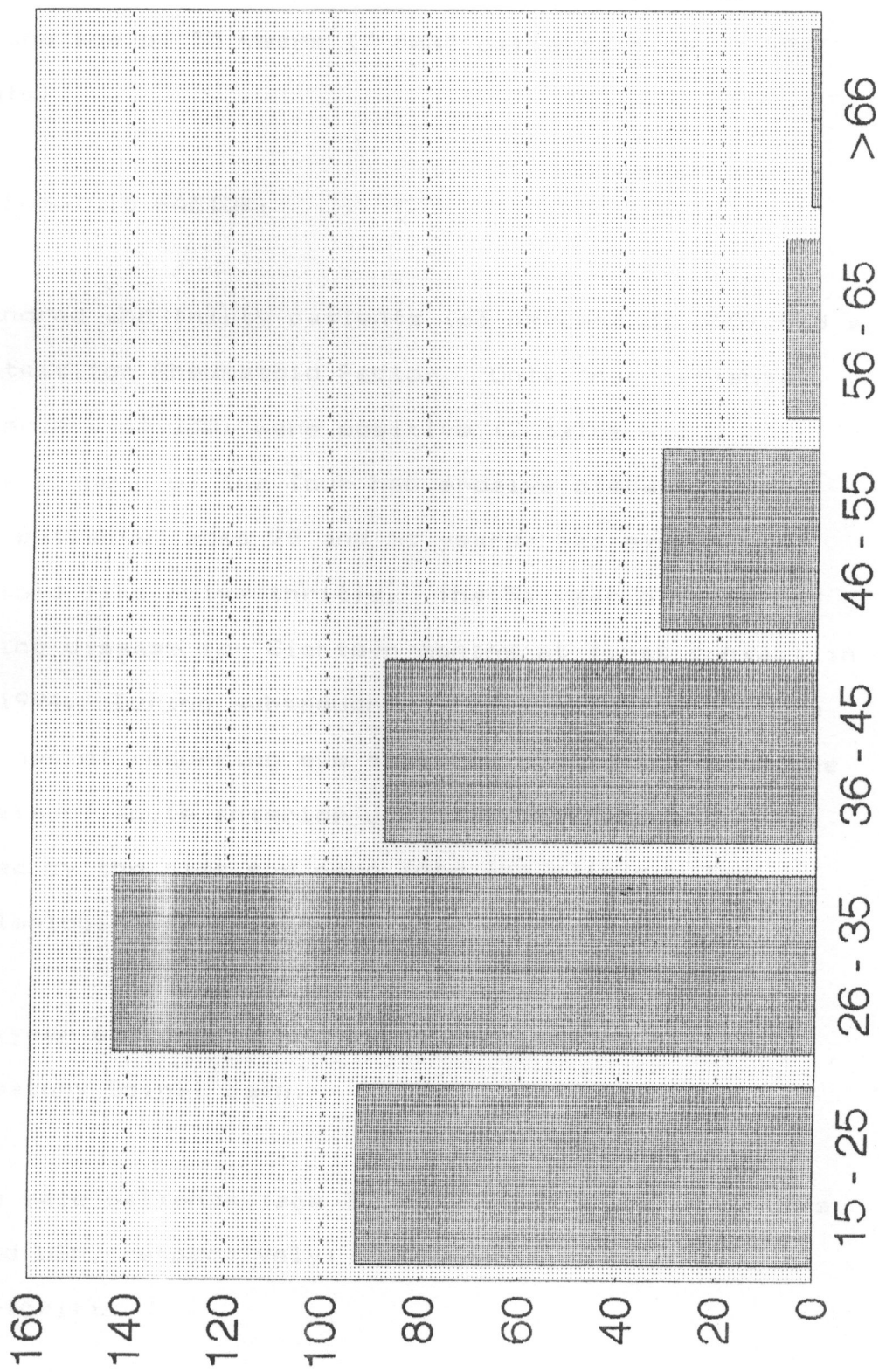
B:2 AGE AND SEX

There were 240 males and 125 females. The mean age was 33 years. This was 30.9 years for the Reactive arthritis group; 33.9 years for the "Arthritis alone" and for the Undifferentiated spondylathritis group; and, it was 37.9 years for the Psoriatic arthritis group (Table II).

TABLE II: SERONEGATIVE ARTHRITIS : SPECIFIC SYNDROMES

SYNDROME	NO. PATIENT S.	AGE MEAN (YR) (RANGE)	M (F)	DISEASE DURATION (MONTHS) (FIRST CONTACT)		MEAN JOINT COUNT (FIRST CONTACT)		% WITH POLYAR- THRITIS AT FIRST CONTACT	HIV POSITIVE PROPORTION
				CURRENT EPISODE	WHOLE	UPPER LIMB	LOWER LIMB		
ARTHRITIS ALONE (AA)	122	33.9 (15-77)	73 (49)	2.6	14.3	1.7	4.0	33	65% OF 91 (M=65%) (F 64%)
REACTIVE ARTHRITIS	119	30.9 (17-54)	(33)	3.0	10.9	3.0	8.2	52	87% OF 99 (M81%) (F100%)
UNDIFFERENTI- ATED SPONDYLARTH- RITIS	112	33.9 (17-60)	72 (40)	4.8	20.0	3.1	7.0	61	98% OF 100 (M 97%) (F 100%)
PSORIATIC ARTHRITIS	11	37.9 (26-54)	08 (03)	14.0	28.9	3.3	5.7	73	91% OF 11 (M88%) (F100%)
ANKYLOSING SPONDYLITIS	01	44	01 (--)	--	--	--	--	--	0 OF 1
TOTAL	365	33.1 (15-77)	240 (125)	3.8	15.3	2.5	6.0	50	84% OF 302

Number of patients



Age group (years)

Figure 1 shows the age of the patients. Eighty-nine percent (324 of 365) of the patients fell in the age stratum 15 to 45 years old. Only nine patients were above the age of 55 years (7 "AA" patients plus 2 "USA" patients).

B:3 RHEUMATOID FACTOR:

Two hundred and thirty patients (63 percent of 365) had a latex test for Rheumatoid Factor. Only four patients (1.7 percent of 230) were positive (2 males and 2 females). None of the four had erosive disease. The female patients (ages 28 and 51 years) had symmetrical Rheumatoid like polyarthrititis. The 51 year old had had relapsing disease for Eighteen months at first contact in June, 1994. During subsequent 17 months follow-up, she complained of recurring eye symptoms consistent with the diagnosis of acute anterior uveitis but these had long resolved by the time she came into the clinic. Two Ophthalmological examinations were unremarkable.

The 28 year old female had associated enthesitis and Inflammatory Spinal pain.

The two male patients (age 30 and 38 years and diagnoses "AA" and USA, respectively) had lower limb oligoarthritis.

All the four patients were seropositive for HIV.

8:4 DISEASE DURATION:

Table II shows the mean duration of the current episode and the whole period since the initial episode of arthritis.

At first contact, the mean duration of the current disease in the 364 patients (i.e. excluding the AS patients) was 4 months; whereas the whole duration of disease was 15 months.

Both duration of current disease and the whole duration were much longer in the Psoriatic group (14 months and 29 months, respectively).

R:5 FAMILY HISTORY

Seven patients had a family member with a history of arthritis. Two male patients with Reiter's syndrome had female relatives with Rheumatoid arthritis (one, his mother; the other his grandmother). The third patient (a 22 year old man with Reiter's disease) had a mother and several maternal aunts with long-standing deforming polyarthritis. The fourth patient was a 28 year old man with USA. His mother and two maternal uncles were afflicted by chronic arthritis. The nature of the arthritis in the relatives of these last two young men could not be varified.

The remaining three patients (two postenteric Reactive arthritis and 1 Reiter's disease) had a sibling each with reactive arthritis.

CI SERONEGATIVE ARTHRITIS: DETAILS OF SPECIFIC SYNDROMES

C: 1: ANKYLOSING SPONDYLITIS:

One 44 year old man satisfied the Modified New York Criteria for Ankylosing Spondylitis (AS) (55).

He had had recurring episodes of low back pain with increasing stiffness at the Lumbar and cervical spines since 1980. Three months before presentation at the clinic, he had developed arthritis of both knees and of the right wrist for the first time.

Examination revealed Limitation of both Lumbar and cervical spine motion in all planes. Radiological features included Asymmetric bridging syndesmophytes in the Lumbar and cervical spines plus grade 3 bilateral sacroiliitis.

This man was HIV-seronegative.

Six patients (4 males and 2 females) had had some of the clinical markers of the disease as defined by the Rome Criteria (59). All six patients reported low back and thoracic pain and stiffness of more than 3 months duration. They all had limited motion of the Lumbar Spine and one male patient had a demonstrable reduction of chest expansion to less than 2.5cm. Three patients had anterior uveitis (2 males and 1 female). Both male patients with uveitis also had Aortic incompetence.

None of the six patients had demonstrable Radiological sacroiliitis although one of the female patients had clinical sacroiliitis at initial contact. This patient also showed squaring of vertebrae and Lytic lesions at the upper anterior corners of several Lumbar Vertebral bodies.

Two male patients also had spinal radiological changes consisting of Vertebral squaring and isolated coarse lateral syndesmophytes on a few thoracic or Lumbar Vertebrae.

All the six patients were HIV - Seropositive. Their clinical features are shown in Table III.

A diagnosis of possible Ankylosing spondylitis was made but since these patients did not meet the pre-defined criteria for the diagnosis of As, they are presented in the following sections under the Reactive arthritis (n=2 and Undifferentiated spondylarthropaty (n=4) diagnostic groups.

TABLE III: PATIENTS WITH ANKYLOSING SPONDYLITIS DEFINING FEATURES

PATIENT NO.	DIAGNOSIS	SEX	AGE	DISEASE DURATION AT:		PAIN AND STIFFNESS		UVEITIS	LIMITED MOTION		SACROILIITIS		SPI-NAL X-RAY CHANGES	EROSIVE PERI-PERAL ARTHRITIS
				FIRST CONT ACT	LAST CONT CT	LUMBAR SPINE	THORACIC		LUMBAR SPINE	CHEST EXPANSION	CLINICAL	X-RAY		
1	USA	F	35	2MON	1YR	++	++	-	++	-	+	-	+	-
2	REA	M	34	5YRS	5½YRS	++	++	++	++	-	-	-	+	+
3	USA	M	31	6½YR	8 YRS	++	++	-	++	++	-	-	+	+
4	REA	M	41	1YR.	2YRS.	++	++	++	++	-	-	-	-	+
5	USA	F	36	5YRS	6YRS	++	++	++	++	-	-	-	-	+
6	USA	M	46	1YR.	1 YR.	++	++	-	++	-	-	-	-	+

F = FEMALE

M = MALE

USA = UNDIFFERENTIATED SPONDYLOARTHRITIS;

REA = REACTIVE ARTHRITIS;

++ = PRESENT

- = ABSENT

* -Indicates a clinical defining feature of Ankylosing Spondylitis according to the Rome criteria (59).
Four patients had four of the five clinical criteria, thereby satisfying the Rome criteria for diagnosis of AS.

C: 2: PSORIATIC ARTHRITIS:

Of the 11 patients with PsA, five experienced an episode of Arthritis before first contact. There had been an accompanying flare in the psoriasis with the onset of arthritis.

Psoriasis preceded arthritis in three patients.

Psoriasis and Arthritis-started concurrently in six patients. In two patients, arthritis preceded the onset of Psoriasis.

In one patient (a 26 year old female), the initial picture was of post-dysenteric reactive arthritis with psoriasis developing 2-3 weeks after onset of arthritis.

Eight patients had polyarticular disease at first contact. There was involvement of the distal interphallangeal (DIP) joints in seven patients.

Two patients had dactylitis and a third one exhibited both Tennis and Golfer's elbow.

Three patients had nail dystrophies (2 males). Ten of the eleven patients (91 percent) were HIV-seropositive.

The only HIV negative patient was a 54 year old man with chronic bilateral knee arthritis which had remitted and relapsed over the previous six years. He had plaque psoriasis involving the trunk and the extensor surfaces of the elbows and knees. He had no nail or x-ray

changes.

The rash was florid in all the HIV -positive patients. In two male patients, the disease was complicated by erythroderma (recurred in one).

Seborrhoea was a common accompaniment and was present to varying degrees in all patients.

The one female patient with nail dystrophies had DIP joint erosions. One other patient (a 41 year old man) had PIP joint erosions on a single finger.

At first contact, Eight patients were in HIV clinical Stage 1, one patient each were in stages 3 and 4. The histories of the last two patients are presented.

Case 1:

The patient in HIV clinical stage 3 was a 41 year old man who had had relapsing disease since 1991. He was first seen in the clinic in July, 1995, with a five months relapse of both the psoriasis and arthritis. He had moderate to severe disease (Arthritis) involving both knees, both ankles, an MTP joint, and the PIP and DIP joints of an index finger. His disease had remained the same despite regular treatment with Indomethacin at 25mg three times a day. He had chronic diarrhoea and fever for 2-3 months. His total Lymphocyte count was 1,300/mm³. His indomethacin dose was increased to 50mg three times a day, to which he responded promptly. He was able to reduce the dose by half after four weeks treatment and to stop completely after six weeks. The patient's general condition continued to deteriorate, however. The diarrhoea worsened and he developed the wasting syndrome, peripheral neuritis and the dementia complex. Arthritis remained in remission to his death in November, 1995. The rash had remained active throughout.

Case2:

The patient in clinical stage 4 was a 36 year old man who developed both psoriasis and arthritis de novo in January, 1994. Three months later he was diagnosed with Pulmonary Tuberculosis (sputum smear positive). In June, he came into hospital with a one week history of epistaxis.

The arthritis had improved markedly at this stage and was not a bother anymore although the rash still was. There was mild residual synovitis of his left ankle joint. simple analgics kept pain under control and he took these as needed.

This patient had disseminated Kaposi Sarcoma lesions over the central portion of his face with lesions in the nostrils and on the hard palate. He was bleeding from an ulcerated lesion in his left nostril. He was treated and followed up at the oncology (tumour) clinic for the malignancy. However, he was reviewed twice in the arthritis clinic over the following two months when his arthritis remained in remission.

C: 2 (a)

THERAPEUTIC RESPONSE:

In general, HIV-positive patients with psoriatic arthritis responded promptly to Indomethacin - all patients reporting improvement within 3-4 weeks of starting therapy and six of nine patients achieving remissions within 4-6 weeks. A more dramatic response occurred in

patients given systemic steroids for severe generalised rash. In such cases, 20mg of Prednisolone once daily given for two weeks produced a gratifying amelioration of both the Psoriasis and arthritis.

C: 2(b)

ENTHESITIS:

Three patients exhibited enthesopathic lesions. Two of the three patients also had sausage digits. All the three were HIV-seropositive.

C: 3: THE ARTHRITIS ALONE, REACTIVE ARTHRITIS AND UNDIFFERENTIATED SPONDYLARTHROPATHY GROUPS

These constituted the largest group contributing 353 patient (69 percent) of this series.

Table II details some of the characteristics of these patients.

There were 231 males and 122 females. The average age was 32.9 years with a range of 15-77 years.

C: 3: (a) DYSENTERY:

Eighty-seven patients (25 percent of 353) had dysentery within one month before onset of arthritis. These included sixteen (33 percent) of the 48 patients with Reiter's disease. In the course of follow-up, an additional twenty-nine patients recorded a bout of dysentery. Features of these patients are detailed in section E 1 below).

C: 3(b) URETHRITIS:

In seven patients (6 males and 1 female), non-gonococcal urethritis preceded the onset of arthritis.

Altogether, therefore, twenty-three (48 percent) of the 48 patients with Reiter's disease had a known preceeding trigger.

C: 3(c) EPISODE BEFORE FIRST CONTACT:

One hundred and eight (31 percent of 353) patients experienced an episode of arthritis before the current episode of disease. There were 70 males and 38 females. They had all made complete recovery from the previous episode (s) with resolution of joint signs.

The initial episode had occurred four months to 10 years before presentation at the clinic with the current episode.

Sixty-two patients (57 percent of 108) had suffered one episode; 15 (14 percent) had had two; while the remaining 31 (29 percent) had had at least three previous episodes.

C: 3(d) JOINT INVOLVEMENT

At initial contact, 59 percent of patients with a previous history of arthritis had polyarticular involvement (i.e. six or more joints involved). In comparison, 45 percent of patients with a first episode of arthritis had polyarticular involvement at first contact.

The mean joint count was 8.5 joints, overall. In the "AA" group, the mean count was 5.7 joints. It was 9.2 joints in the ReA group and 10.1 joints in the USA group.

Table IV shows the pattern of joint involvement.

There was predominant lower limb involvement with the following pattern of limb involvement:-

- (i) Upper Limb Alone in 2 percent of patients
- (ii) Lower Limb Alone in 22 percent of patients
- (iii) Both Limbs in 76 percent of patients.

The knee joint was the most frequently involved individual joint, being affected in 82 percent of patients. It was followed by the ankle, MTP, and Tarsal joints which were affected in 56%, 46% and 31% of patients, respectively.

The wrist joint was the most frequently affected upper limb joint. It was affected in 26 percent of patients, making it the fifth most frequently affected joint overall.

Hip joint involvement was uncommon (3 percent of patients), clinical sacroiliitis was present in 1.7

TABLE IV: SERONEGATIVE ARTHRITIS : PATTERN OF JOINT INVOLVEMENT

JOINT	% OF PATIENTS WITH JOINT INVOLVED (n = 290)	JOINT COUNT	
		HIV + (n = 193)	HIV - (n = 34)
TEMPORO-MANDIBULAR	2.4	05	01
STERNO-CLAVICULAR	2.8	12	00
ACROMIO-CLAVICULAR	7.2	17	01
SHOULDER	10.0	33	03
ELBOW	15.2	44	10
WRIST	28.3	91	09
METACARPO-PHALANGEAL	22.8	157	10
FINGER P.I.P	23.4	171	07
FINGER D.I.P	10.0	52	01
SACROILIAC	1.7	04	00
HIP	3.1	14	01
KNEE	81.7	244	45
ANKLE	56.2	207	22
TARSAL	31.0	118	14
METATARSO-PHALANGEAL	45.5	555	27
TOE PIP	22.1	214	01
TOE DIP	6.9	64	00
	MEAN COUNT	10.4	4.5

percent of patients. There were more patients with finger PIP and Finger DIP joint involvement than there were patients with Toe PIP and Toe DIP joint involvement respectively. However, when the toe joints were affected, the counts were often greater than the corresponding counts of finger joints.

C: 3 (e) ENTHESTITIS:

One hundred and eighty-two patients (52 percent) of the 353 exhibited an enthesopathy in the course of their disease. These consisted of 112 "USA" patients and 70 "ReA" patients. There were 123 males and 59 females.

Table V shows the frequency of involvement of individual entheses at initial contact and in the course follow up.

Achilles tendonitis was present in 16 per cent (46 of 290) patients at first contact. In the course of follow-up, another twenty-one patients developed the lesion, making the overall frequency of occurrence 23 per cent.

Plantar fasciitis was found in 40 (or 14 percent) of patients in the course of follow-up (present at initial contact in twenty-nine and developing later in another eleven patients).

Sixteen patients had both achilles tendonitis and plantar fasciitis. The number of patients exhibiting Achilles tendonitis and/or planter fascitis in the course of their disease, therefore, was Ninety-one ($46 + 21 + 29 + 11 = 107$) or 31 percent of the 290 patients.

TABLE V : SERONEGATIVE ARTHRITIS : PATTERN OF ENTHESOPATHIES IN 290 PATIENTS

ENTHESOPATHY	% PATIENTS WITH LESION (FIRST CONTACT)	% PATIENTS WITH LESION (FOLLOW-UP)
ACHILLES TENDONITIS	15.9	23.1
PLANTAR FASCITIS	10.0	13.8
TENNIS ELBOW	8.6	12.8
GOLFER'S ELBOW	1.0	1.7
FEMORAL AND/OR TIBIAL CONDYLES	7.6	14.1
MEDIAL AND/OR LATERAL MALLEOLI	8.3	10.0
TIBIAL TUBEROSITY	4.5	9.0
FIBULA HEAD	2.4	3.8
NUCHAL CREST AND/OR CERVICAL SPINOUS PROCESSES	4.1	7.6
TENDONITIS	6.6	13.4
CHONDRITIS	2.4	4.1
ISCHIAL TUBEROSITY AND/OR FEMORAL GREATER TROCHANTER	1.0	2.4
PERIOSTITIS	2.4	9.0
ANTERIOR SUPERIOR ILIAC SPINES	1.4	1.4
SAUSAGE DIGITS (DACTYLITIS)	8.6	10.7

Periostitis was observed in twenty-six patients (9 cent cent of 290) in the course of their disease. The lesions include Painful and Tender/Swollen Heels (11 patients); Painful and Tender clavicular shaft-usually unilateral (8 patients); Pain and Tenderness of the lower third of the Tibiae (5 patients), Pain and Tenderness/swelling of the Metatarsal and Metacarpal shafts (2 patients).

The syndrome occurrence of enthesitis was as follows: 100 percent (112 of 112) of patients with USA; 59 percent (70

[S] 28/3,10/90 Diclofenac Na 50mg Misoprostol 200mcg

of 119) of patients with ReA as a whole and 67 percent (32 of 48) of patients with Reiter's disease.

The occurrence of enthesitis by Episode of arthritis was as follows: Sixty-one of 108 patients with disease recurrence (i.e. 56 percent) and 121 (49 percent) of 245 patients with their first episode of arthritis. These prevalences are not statistically different ($\chi^2=1.5102, P>0.20$; ODDS RATIO =0.75).

D: SERONEGATIVE ARTHRITIS: ASSOCIATIONS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION.

Two hundred and ninety of the 353 patients with "AA", ReA, and USA were tested for HIV and 84 percent (245 of 290) were HIV-seropositive (95% confidence interval 79.7 to 88.3 percent: $P=0.05$).

D: 1: HIV-SEROPREVALENCE BY DIAGNOSTIC SYNDROME

Table II shows the HIV-seroprevalence by diagnostic group. It was lowest (65 percent) in the "ARTHRITIS ALONE" group. Seroprevalence was 87 percent in the Reactive Arthritis group and 98 percent in the Undifferentiated spondyloarthropathy group.

D 2: HIV-SEROPREVALENCE BY AGE AND SYNDROME

Figure 2 shows the HIV-seroprevalence by age group and diagnostic syndrome.

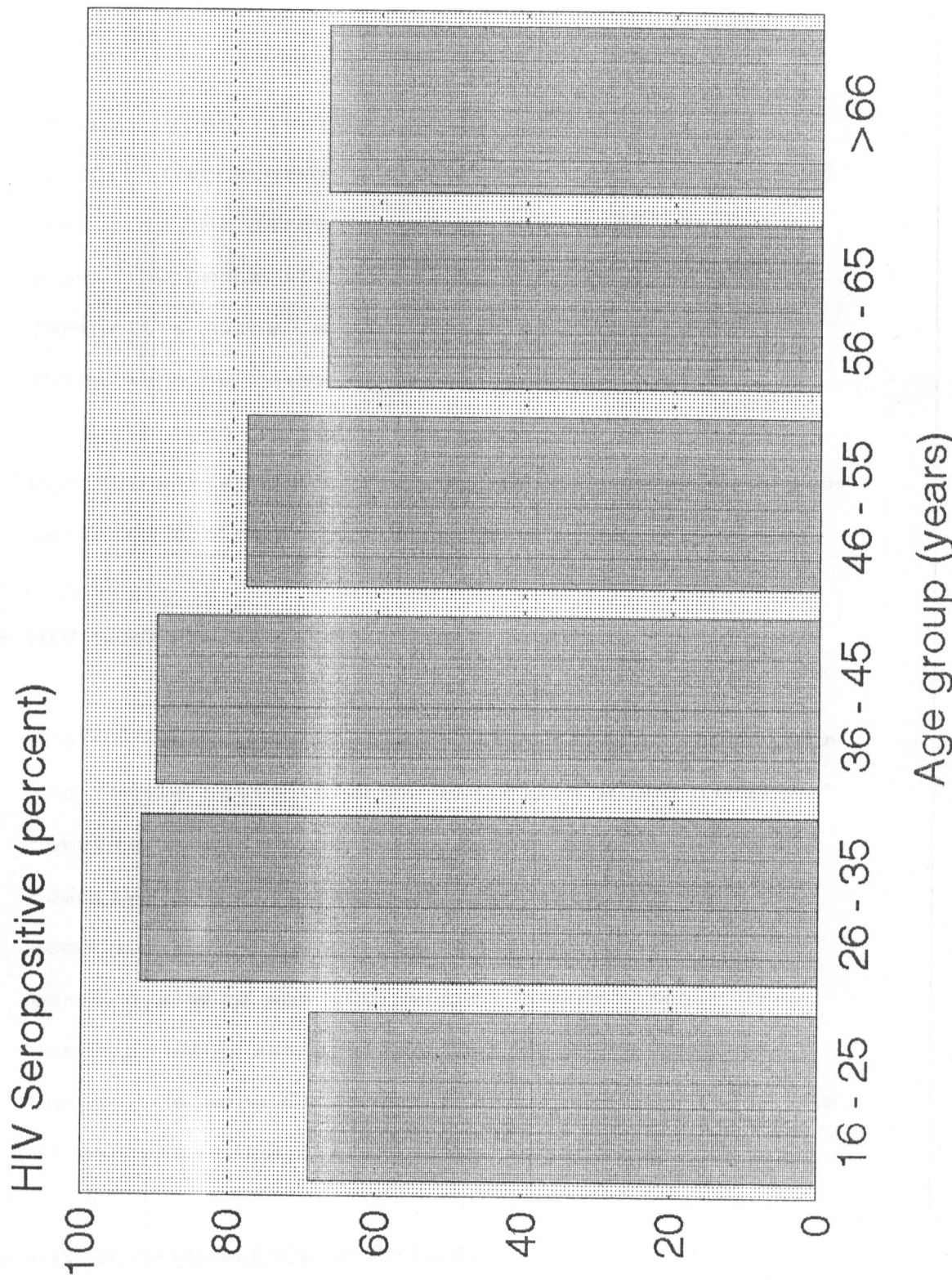
D 2 (i) AGE PREVALENCE:

The Seroprevalence rose sharply from 69 percent in the age group 15-25 years to peak at 92 percent in the 26-35 years age range. There was then a progressive decline in the seroprevalence from 90 percent in those 36-45 years of age to 78 percent in the 46-55 years group. The seroprevalence was 67 percent in the age group 56-65 and in those 66 years and older.

D 2 (ii): AGE-SYNDROME PREVALENCE:

The HIV-seroprevalence remains highest in the USA diagnostic group at all age groups except the 46-55 years age group where one of eight patients was HIV-

Age - Specific HIV Seroprevalence in 290 patients



sero-negative. Two patients in the 56-65 years age group with USA were both seropositive.

In the "Arthritis Alone" diagnostic group, the HIV seroprevalence were significantly less in the 15-25 year olds (46 percent) and in the 46-55 years age group (50 percent).

"Arthritis Alone" was found at all age groups.

There were no cases of Reactive Arthritis in patients aged 56 years and over, and no case of Undifferentiated Spondylarthropathy in patients aged 66 years and over.

D 3: HIV SEROPREVALENCE BY SEX:

The HIV-seroprevalence were identical for both male and female patients with "Arthritis Alone" (65 percent versus 64 percent, respectively). In the Reactive arthritis and Undifferentiated Spondylarthropathy groups, however, the HIV-seroprevalence was 100 percent among women. The corresponding seroprevalences for men with these conditions were 81 percent (Reactive arthritis) and 97 percent (Undifferentiated spondylarthropathy).

D 4: HIV-SEROPREVALENCE BY EPISODE

The HIV-Seroprevalence among patients with a first episode of arthritis was 80 percent (160 of 200 patients). The Seroprevalence was significantly

higher (92 percent) of patients) among patients with a previous history of arthritis.

Among patients with the first episode of arthritis seen within one month of onset, the HIV-Seroprevalence was much lower (67 percent: 50 of 75 patients: 95% C.I. 56-78%; $P=0.5$) compared to the 84 percent seroprevalence for seronegative arthritis group as a whole and in comparison to the 80 percent Seroprevalence among patients with a first episode of arthritis in general.

E: SERONEGATIVE ARTHRITIS: CLINICAL FEATURES

In this section, the clinical features of patients with "Arthritis Alone", Reactive", Reactive Arthritis and Undifferentiated spondylarthropathy are reviewed in the context of the HIV Serostatus.

E 1: DYSENTERY:

Of the 87 patients who experienced a preceding bout of dysentery 74 were HIV - tested and sixty-three (85 percent of 74) were Seropositive.

When this result is viewed from the point of view of the whole group (i.e. "AA", ReA and USA, combined), the proportions of patients reporting a preceding bout of dysentery are not significantly different (26 percent of 243 HIV-positive versus 23 percent of 47 HIV-negative patients, $\chi^2=0.1318$; $P=0.7$; ODDS RATIO = 1.1). Again, when viewed from the context of the Reactive arthritis

group alone the proportions of HIV positive and HIV-negative patients reporting a preceding bout of dysentery were not significantly different (73 percent of 86 patients versus 35 percent of 13 patients, respectively, χ^2 with Yates correction=0.2875, $P=0.6$; ODDS RATIO =0.5).

However, the occurrence of a dysenteric illness subsequent to the onset of arthritis appears to occur exclusively in the context of HIV infection. Of the twenty-nine patients that developed bloody diarrhoea following the onset of arthritis, twenty-eight were tested for HIV antibodies and they were all seropositive.

The dysenteric illness set in a few weeks to several months following onset of arthritis. The symptoms occurred independently of intake of non-steroidal antiinflammatory drugs and so could not possibly be attributed to them. Constipation often alternated with short episodes of bloody diarrhoea.

The onset of diarrhoea was usually explosive with moderate to large quantities of bloody stools but settling quickly within 1-2 days. In one third of this population of patients there was chronic passage of small quantities of stool mixed with blood and mucus.

Stool cultures were repeatedly negative. Clinically, 15 patients belonged to the USA group: 9 to the Reiter's syndrome group; and 2 (one HIV tested) to the AA group.

Lower gastrointestinal endoscopic studies were not feasible during the study period but are planned.

It seems probable that this group of patients may not be cases of infective dysentery but rather their symptoms may be the result of gastrointestinal involvement (a colitis) either accompanying the spondylarthropathy or directly related to HIV infection. In this context there are intriguing similarities with the arthritis associated with ulcerative colitis or crohns disease (so called enteropathic arthropathy and included in the spectrum of spondylarthropathies).

REACT (anti) Pirfenone Na 50mg Misoprostol 200mcg

E1: (a) Case History:

One patient (a 34 year old with Reiter's syndrome of 5 year's duration) had had recurring short bouts of bloody diarrhoea following relapses of arthritis in the first two years of his disease. Subsequently, the bowel symptoms became more severe and a prominent feature of his disease. He had recurring exacerbations of fever, abdominal pain and diarrhoea with foul-smelling stools with blood and mucus. This patient had severe erosive Polyarthrititis, Aortic regurgitation, Keratoderma blenorrhagicum, Uveitis and isolated bony spurs at a few Lumbar vertebral bodies. His bowels and arthritis symptoms responded promptly to Sulphasalazine 1gram daily. He could walk without clutches for the first time in more than half a year within six weeks of starting treatment. Unfortunately, he developed Infective Endocarditis in the third month of treatment and owing to accompanying nausea and vomiting, he terminated Sulphasalazine therapy. Explosive bowel symptoms relapsed within two weeks but the arthritis did not. Despite treatment, his condition deteriorated progressively. He developed acute renal failure and died two weeks following admission to hospital.

E2: URETHRITIS: Six of the seven Reiter's Disease patients who had Urethritis prior to onset of arthritis were HIV - tested and 4 were Seropositive. This means, therefore, that all the thirteen HIV-negative patients with Reactive arthritis had an identifiable preceding trigger,

whereas nineteen HIV-positive patients in this diagnostic group did not report such preceding trigger infection.

E3: FEVER: Fever was a common accompanying complaint at onset of disease or during exacerbations. An axillary Temperature of at least 38 degrees Celcius was documented in 62 per cent of Fifty-three patients presenting within two weeks of onset of arthritis.

In twenty-three patients (6.5 per cent of 353), however, an acute febrile illness preceded the onset of arthritis by a few days to about two weeks. The febrile illness was either getting better or had resolved completely when arthritis set in. All of eighteen patients that were tested from this group were HIV-seropositive.

The febrile illness was treated as Malaria in all of them and there was a supporting positive Malaria parasite slide in six patients.

At initial contact in the Arthritis Clinic, Sixteen of the 18 patients were in HIV clinical stage 1 (PGL = 2 patients : ASYMPTOMATIC = 14 patients); Two patients were in HIV stage 3, both having suffered from Pulmonary Tuberculosis within a year of presentation at the clinic.

E4: JOINT INVOLVEMENT: Table IV shows the patter of joint involvement in patients with AA, ReA, and USA.

Firstly, the table shows the per centage of the 290 patients in whom a particular joint was affected. Secondly, it shows the joint counts in HIV-positive and HIV-negative patients.

E4 (i): PATTERN: The pattern of joint involvement was

the same in both HIV-positive and HIV-negative patients, being a predominant lower limb disease in both with the upper limb and lower limb joints being affected in a ratio of approximately 1:3 (table VI). However, the disease tended to be polyarticular in the HIV-positive patients and mean joint count in this population of patients was 10.4 joints compared to 4.5 joints in the HIV-negative population. The proportion of patients with polyarthrititis at first contact among the HIV-positive patients was significantly higher than that among the HIV-negative patients (59 per cent of 243 HIV positive patients versus 34 per cent of 47 HIV-negative patients, $\chi^2 = 9.7840$, $P < 0.01$; ODDS RATIO = 3).

E4 (ii): PROGRESSION: Exacerbation of disease and an increase in the total joint count occurred in the course of follow-up in the current episode of disease in 28 per cent of the 243 HIV-positive patients compared to 13 per cent of the 47 HIV-negative patients $\chi^2 = 4.7985$, $P < 0.05$; ODDS RATIO = 3). As a result of this, twenty-two of 88 HIV-positive patients and one of 27 HIV-negative patients who had Oligoarticular disease at initial contact developed polyarticular involvement. The proportion of HIV-positive patients developing polyarthrititis in the course of follow-up was significantly greater than could be accounted for by chance (i.e 22 of 88 HIV-positive patients versus one of 27 HIV-negative patients, corrected $\chi^2 = 4.6011$, $P < 0.05$, ODDS RATIO = 8.7).

TABLE VI: SERONEGATIVE ARTHRITIS: CLINICAL FEATURES OF SERO-POSITIVE AND SERO-NEGATIVE PATIENTS AT INITIAL CONTACT.

HIV SERO- STATUS	NO	MEAN AGE(YRS (RANGE)	M(F)	DURATION IN MONTHS (MEAN)		MEAN JOINT COUNT		PATTERN JOINT INVOLVEMENT	
				THIS EPISODE	WHOLE	UPPER LIMB	LOWER LIMB	OA	PA
POSI- TIVE	243	33.2 (17-70)	154(89)	3.9	17.5	3.0	7.8	41%	59%
NEGA- TIVE	47	30.9 (16-77)	34(13)	2.6	8.1	1.2	3.2	66%	34%

OA = OLIGOARTICULAR

PA = POLYARTICULAR

E4 (iii): JOINT INVOLVEMENT IN PATIENTS WITH THE FIRST
EPISODE OF ARTHRITIS.

There were 160 HIV positive and 40 HIV-negative patients with their first episode of arthritis. In six HIV-positive and in three HIV-negative patients, disease was polyarticular from onset (i.e. at least six joints affected within one to two weeks of onset). The difference between these proportions was not statistically significant (corrected $\chi^2 = 0.3563$, $P > 0.50$; ODDS RATIO = 0.48).

At first contact, 12,5 per cent of HIV positive patients and 7.5 per cent of HIV negative patients had Monoarthritis. These proportions were not significantly different. The mean duration of disease was also comparable in the HIV-positive and HIV-negative patients (1.9 months and 2.1 months, respectively).

There were significantly more HIV-negative than HIV positive patients with 2-5 joint involvement (57.5 per cent and 32.5 per cent, respectively). In this category of joint involvement the mean disease duration was 3 months for the HIV-positive patients and 2.2 months for the HIV-negative patients. Note the one and half times increase in the mean disease duration in the HIV-positive population from the corresponding figure of 1.9 months among patients with Monoarthritis to the duration of 3 months in those with 2-5 joints affected. The mean duration in the HIV-negative patients remains essentially the same (2.1 months in patients with Monoarthritis and 2.2 months in patients with

2-5 joint involvement).

Fifty-five per cent of the 160 HIV positive patients had polyarticular involvement at first contact compared to 35 per cent of 40 HIV negative patients (corrected $\chi^2 = 4.3530$, $P < 0.05$; ODDS RATIO = 2.3). The increasing trend in the mean disease duration is maintained in the HIV positive population, increasing to 4.7 months in the polyarthrititis subpopulation from 3 months in those with 2-5 joint involvement. The mean duration of disease in HIV negative patients with polyarticular involvement remained as in the other two joint strata at 2.1 months.

These data on joint involvement in patients with their first episode of disease confirm the progressive nature of the disease in HIV-infected patients even prior to initial contact. One other fact emerges, and this is that the static mean disease duration in HIV-negative patients at all three strata of joint involvement suggests that polyarticular involvement in the HIV-negative patients, if it is going to occur, will occur soon after onset of the disease.

E5: EPISODE BEFORE DIAGNOSIS: The proportion of patients with disease recurrence and the HIV-seroprevalence with recurrent disease have been dealt with in sections C3(c) and D4, respectively. In this section, the points of difference between HIV-positive and HIV-negative patients with recurrent disease at first contact are highlighted.

E5 (i): PREVALENCE: Eighty-three of the 243

HIV-positive patients (34 per cent) had had an episode of arthritis before the current one at initial contact. In comparison only seven of the 47 HIV-negative patients had had an episode of arthritis before first contact. The difference in the proportion of patients with recurrent disease among the HIV-positive and the HIV-negative patients was larger than could be expected to occur by chance ($\chi^2 = 6.8276$, $P < 0.01$: ODDS RATIO = 3).

E5 (ii): JOINT INVOLVEMENT IN PATIENTS WITH DISEASE

RECURRENCE:

Sixty-seven per cent of 83 HIV positive patients with disease recurrence had polyarticular disease at initial contact. The proportions with 2-5 joints affected and Monoarthritis among the HIV-positive patients were 29 per cent and 4 per cent, respectively.

Among the seven HIV-negative patients with disease recurrence, two had polyarthritis, three, 2-5 joints affected; and, two had Monoarthritis. The numbers of HIV-negative patients with disease recurrence were very small for meaningful comparison with the HIV-positive patients.

Of the eighty-three HIV-positive patients with disease recurrence, 46 had had one previous episode while the remaining thirty-seven had had at least two previous episodes. The proportion of patients with polyarticular disease among patients with one previous episode was 63 per cent, where as it was 73 per cent among patients who had had

at least two previous episodes of disease.

These data on disease recurrence confirm the Relapsing nature of the HIV-associated disease as well as highlight the progressive nature of the disease as demonstrated by the rising proportion of patients with polyarticular disease with subsequent relapses.

E6: ENTESITIS: The spectrum and syndrome occurrence of enthesitis has been considered in section C3(e). Under the present section, the characteristics of enthesitis in HIV-infected and non HIV-infected patients will be compared. Of the 182 patients with enthesitis, 162 were HIV-tested, and 153 (94 per cent) of these 162 patients were HIV-seropositive. The association between HIV-infection and enthesitis was overwhelming. Whereas 153 of the 243 (63 per cent) HIV positive patients had enthesitis, only nine of the 47 (19 per cent) HIV-negative patients exhibited this lesion ($\chi^2 = 30.6622$, $P < 0.001$; ODDS RATIO = 7.2).

Unlike polyarthrititis, there was no difference in the prevalence of enthesitis among HIV-positive patients with disease recurrence and those with their first episode of disease (63 per cent in both groups i.e 52 of 83 patients with disease recurrence and 101 of 160 patients with first episode of disease; $\chi^2 = 0.0053$, $P > 0.9$, ODDS RATIO = 1.0). Put in another way, this finding suggests that enthesitis in HIV-positive individuals with a spondylarthropathy is as likely to occur in the first episode as in subsequent episodes.

Of the nine HIV-negative patients (all male) with enthesitis seven were having their first episode of arthritis while the remaining two had had previous episodes of arthritis. Six patients had a recognisable preceding trigger infection.

The clinical characteristics and the enthesopathic lesions in the nine HIV-negative patients are shown in Table VII.

In comparison, HIV-negative patients tended to have more transient non-recurrent pauci - enthesitis whereas the opposite was the usual character of enthesitis in HIV-positive patients.

E7: UROGENITAL, OCULAR, ORAL, INTEGUMENTARY AND CARDIAC LESIONS.

The spectrum of lesions that were encountered are listed in Table VIII. They tended to occur more often or exclusively in HIV-positive patients. This however, may merely be a reflection of the fact that spondylarthropathic disease occurred almost exclusively in HIV - positive persons (i.e. 184 of the 199 patients with a diagnosis of ReA and USA). Nevertheless, the fact that these lesions were observed in this population of patients is remarkable as it confirms the similarity between the HIV - associated spondylarthropathies in black Africans and the conventional disease described in HLA - B27 positive caucasians.

Two of the eight patients with onycholysis did exhibit transient superficial pitting of a single nail each. Six patients (2 male and 4 female) experienced recurring transient paroxysms of palpitations. In five of them

TABLE VII: CHARACTERISTICS OF HIV-NEGATIVE PATIENTS WITH ENTHESOPATHIES

SERIAL	AGE(YR)	SEX	DX	TRIGGER FACTOR(S)	ENTHESOPATHIC LESIONS (S)
1	18	M	RS	UNKNOWN	GOLFER'S ELBOW (UNILATERAL)
2	19	M	RS	URETHRITIS	ACHILLES TENDONITIS (UNILATERAL)
3	20	M	RS	DYSENTERY	.CERVICAL SPINOUS PROCESSES .NUCHAL CRESTS
4	41	M	R E A	DYSENTERY	.ACHILLES TENDONITIS (UNILATERAL) .BILATERAL PLANTAR FASCIITIS .MEDIAL MALLEOLI
5	17	M	R E A	DYSENTERY	. SAUSAGE DIGITS . RIGHT TENNIS ELBOW
6	19	M	R E A	DYSENTERY	. BILATERAL PLANTAR FASCIITIS . LEFT TENNIS ELBOW
7	17	M	R E A	DYSENTERY	. BOTH MEDIAL MALLEOLI . RIGHT MEDIAL MALLEOLUS
8	39	M	USA	UNKNOWN	. ALL FEMORAL AND TIBIAL CONDYLES . ALL MALLEOLI . A FIBULA HEAD
9	53	M	USA	UNKNOWN	. BILATERAL ANTERIOR SUPERIOR ILIAC SPINE . TENDONITIS

DX = DIAGNOSIS

RS = REITER'S SYNDROME

R E A = REACTIVE ARTHRITIS

USA = UNDIFFERENTIATED SPONDYLARTHROPATHY

TABLE VIII : OCCURRENCE OF UROGENITAL, OCULAR, ORAL,
INTEGUMENTARY AND CARDIAC LESIONS

LESION	IN WHOLE SERIES' PATIENTS	IN HIV-TESTED PATIENTS	
		HIV POSITIVE	HIV - NEGATIVE
URETHRITIS	21 (17M:4F)	14 (11M:3F)	02 BOTH MALE
CYSTITIS	03 (2M:1F)	02 BOTH MALE	--
PROSTATITIS	02	02	--
BALANITIS	12	10	--
CERVICITIS	02	02	--
VULVITIS	02	02	--
CONJUCTIVITIS	23 (15M:8F)	19 (11M:8F)	01 MALE
UVEITIS	11 (5M:6F)	10 (4M:6F)	--
BUCCAL ULCERATION	08 (6M:2F)	08 (6M:2F)	--
KERATODERMA BLENORRHAGICUM	07 (6M:1F)	07 (6M:1F)	--
ONYCHOLYSIS	08 ALL MALE	08 ALL MALE	--
ERYTHERMA NODOSUM	07 (1M:6F)	07 (1M:6F)	--
PERICARDITIS	02 (1M:1F)	02 (1M:1F)	--
AORTIC REGURGITATION	02 BOTH MALE	02 BOTH MALE	

Electrocardiograms (done in "normal" state) and the physical examination revealed no abnormality. In the sixth patient (a female) the symptoms were more persistent and she had a sustained tachycardia.

This woman had also suffered from Vulvitis and anterior uveitis. An Echocardiogram revealed a very thick pericardium with a small Pericardial effusion.

Both patients with regurgitation had complicating infective endocarditis. One of them died (his case history has been presented under section E1). The other patient a 41 year old man, recovered from the infection. He remains on maintenance anti-heart failure drug therapy. Because of anxieties engendered by his HIV-status, he has been empirically put on a prophylactic regimen of Amoxycillin 250mg QID for 5 days to be taken whenever he develops a bout of diarrhoea. This is in addition to monthly Benzanthine Penicillin injections.

E8: RADIOLOGICAL FEATURES: Many patients had radiographs of their joints taken in the Casualty or Clinics before they came to the Arthritis Clinic. These films were mostly of the large lower limb joints and there were over a hundred knee X-Rays of both HIV - positive and HIV - negative patients. Except for mild periarticular osteoporosis in a few of them there were no remarkable abnormalities.

In the clinic, we undertook to take X-Ray Films of persistently symptomatic or deformed joints. We took spine

and sacroiliac X-Ray pictures in patients with persistent backache, clinical sacroillitis or restriction in spine motion. None of the HIV - negative patients satisfied these criteria and so the changes described here pertain to the HIV - positive patients. Persistent synovitis of the large joints was rare. Unremitting pain around the knee and ankle joints was usually from enthesopathies. Knee X-Rays in five patients with persistent enthesitis around this joint showed marked osteoporosis confined to the tibial tuberosities and the femoral and Tibial condyles. In two of these patients there was erosion and roughness of the patella insertion of the patella tendon.

One patient (a 28 year old female) had erosive disease of a hip joint in addition to erosive disease of hand and foot joints.

Persistent disease in HIV - positive patients affects predominantly the wrist and Tarsal joints and the small joints of the feet and hands. Radiological changes included periarticular osteoporosis, Erosions, subluxation and Ankylosis of these joints as well as periostitis and Enthesitis. Examples of these lesions are illustrated in Appendices I to VII.

E9: TREATMENT: Complete follow-up is inherently difficult in a population of patients where hospital visits are only necessitated by the presence or persistence of symptoms. To accommodate this fact, we could not set a uniform duration for evaluation of therapeutic response.

Useful information is obtained, however, from an evaluation of the therapeutic state of the patient at the last clinic visit. The variables available for analysis are then the number of patients in a particular therapeutic category and the duration of time they have been on treatment for.

Table IX shows the therapeutic status of 173 HIV positive and thirty-one HIV - negative patients at their last clinic visit.

The proportion of HIV - positive and HIV - negative patients in the Remission, Improved and Unimproved categories are not significantly different from each other (χ^2 0.7472, $P > 0.3$; χ^2 1.3694 ; $P > 0.2$, and χ^2 1.4976, $P > 0.2$, respectively). The HIV - positive patients at every category of therapeutic response had been on treatment for longer than their HIV - negative counterparts, however.

Two other facts are notable. Firstly, whereas Ten per cent of HIV - positive patients relapsed, no such event was recorded in the HIV - negative population.

Secondly, whereas the treatment duration was comparable at all levels of therapeutic response in the HIV - positive population, the duration of treatment was much longer in HIV - negative patients in clinical remission than in those recording improvement which was in turn much longer than the duration in the unimproved patients. These results show that while the disease in HIV - negative patients improves progressively with time, there is no such linear time-response relationship in HIV - positive patients.

TABLE IX: THERAPEUTIC STATE AND DURATION OF TREATMENT AT LAST CONTACT

THERAPEUTIC STATE	HIV - POSITIVE (n=173)		HIV - NEGATIVE (n=31)	
	NUMBER (%) OF PATIENTS	DURATION TREATMENT	NUMBER (%) OF PATIENTS	DURATION TREATMENT
REMISSION	30 (17%)	35.8 WEEKS	08 (26%)	24.9 WEEKS
IMPROVED	83 (48%)	32.8 WEEKS	19 (61%)	19.5 WEEKS
RELAPSE	17 (10%)	--	00	--
UNIMPROVED	43 (25%)	31.7 WEEKS	04 (13%)	12.6 WEEKS

It is, therefore, justifiable at this stage to state that the disease in HIV - positive patients tends to be persistent and likely to Relapse while the disease in HIV - negative patients tends to be Remitive.

F: SERONEGATIVE ARTHRITIS: CLINICAL FEATURES OF HIV-POSITIVE PATIENTS.

In this section the clinical features of HIV-positive patients with "Arthritis Alone," Reactive Arthritis and Undifferentiated Spondylarthropathy are evaluated.

Particular note is taken of the HIV clinical stage and of its change with time in patients belonging to the three diagnostic groups. The effect of HIV clinical stage on therapeutic result is also noted.

F1: THE HIV - CLINICAL STAGE AT FIRST CONTACT.

Table X shows the HIV Clinical stage (WHO) of the 243 HIV - positive patients at entry to the study.

Eighty per cent of patients in each diagnostic group were in clinical stage 1. The proportions in clinical stage 2 and 3 are comparable and there were no patients in HIV stage 4. Within the group of patients in clinical stage 1, however, the proportions of patients with persistent Lymphadenopathy (PGL) in the ReA and USA groups are much higher than in the "AA" group.

Seronegative arthritis, therefore, occurs early in the course of HIV infection but patients with ReA and USA seem to be in a slightly more advanced phase of HIV infection than the "AA" patients as suggested by the Lymphadenopathy

TABLE X: HIV CLINICAL STAGE (WHO) AT FIRST CONTACT BY
DIAGNOSTIC CATEGORY

HIV CLINICAL STAGE (WHO)	AA	R e A	USA	TOTAL
1	47 (80% OF 59) PGL = 09	69 (80% OF 86) PGL = 25	78 (80% OF 98) PGL = 31	194 (80% OF 243)
2	02 (3% OF 59)	06 (7% OF 86)	02 (02% OF 98)	10 (4% OF 243)
3	10 (17% OF 59)	11 (13% OF 86)	18 (18% OF 98)	39 (16% OF 243)
4	00	00	00	00
TOTAL	59 (100%)	26 (100%)	98 (100%)	243 (100%)

data.

F2: HIV - DEFINING FEATURES: Persistent Generalised

Lymphadenopathy (PGL) was present at first contact in seventy-three patients. In another fifteen patients, PGL developed in the course of follow-up.

Eleven patients had Herpes Zoster prior to onset of arthritis. In another two patients, Herpes Zoster developed after onset of Arthritis.

Fourteen patients had Pulmonary Tuberculosis prior to onset of arthritis. In another four patients, tuberculosis developed concurrently with arthritis; in yet another four patients, tuberculosis developed subsequent to the onset of arthritis.

First occurrence of seronegative arthritis in the context of chronic diarrhoea and the HIV/AIDS - wasting syndrome is uncommon, occurring in only six (2.5 per cent) of the 243 HIV - positive patients in this series. Corroborative evidence in support of this fact is provided by the virtual absence of inflammatory arthritis in the population of hospital patients with chronic diarrhoea and the wasting syndrome (unpublished observations).

What is more, the arthritis in the chronic diarrhoea patients tended to be short-lived, responding promptly to non-steroidal anti-inflammatory drugs. Illustrative cases of patients with arthritis occurring on the background of chronic diarrhoea are presented.

Case 1: A 40 year old man with diarrhoea of 8 months

duration developed fever and a dry cough in October, 1994. An X-Ray of the chest taken in late December, 1994 looked suspicious and he was started on Anti-Tuberculosis therapy. Two weeks later, he developed arthritis of his shoulder joints, inflammatory spinal pain and anterior chest pain. These symptoms worsened rapidly and so he was transferred to the University Teaching Hospital from the Kitwe Central Hospital. Examination confirmed the shoulder arthritis and also revealed severe Costo-chondritis with loosening of ribs at some cost-chondral junctions. He was also tender and stiff in the Dorsal and Lumbar spines. Arthritis resolved within one week of treatment with Indomethacin 50mg TID and the chondritis in two and half weeks. Spinal pain and tenderness remained significant over the next four months follow-up. There were no notable X-Ray changes. His general condition deteriorated rapidly and he died in May, 1994.

Case 2: A 40 year old man with a history of Diarrhoea and Fever of more than 6 months' duration was admitted to hospital with a two week history of arthritis. He was bedbound with polyarthritis involving the left wrist, both knees (with effusions), both ankles, and all MTP joints (bilaterally). Indomethacin 50mg TID produced dramatic resolution of symptoms. He was ambulant and could be discharged from hospital on the third day of admission. He was asymptomatic on half the dose of Indomethacin at review two weeks later and he was able to terminate his treatment

completely one week later.

Case 3: A 38 year old woman with a long - standing history of diarrhoea and currently on treatment for sputum smear positive Pulmonary Tuberculosis was admitted to hospital in July, 1994 with moderately severe lower limb arthritis of one week's duration and upper limb arthritis for one day. She had polyarthrititis involving both knees (with effusions), both ankle joints, all MTP joints on the Right, the Left elbow and the Left wrist joints. She also had painful sensory neuropathy with paraesthesiae and burning pain in toes and soles of feet. The arthritis resolved completely within one week of starting Indomethacin therapy. She remained incapacitated by the neuropathy, however.

Case 4: A 54 year old widow was seen in the clinic with a 3 months' history of polyarthrititis in February, 1995. She had previously been admitted to hospital with shigella Dysentery enteritis in September, 1992; Multidermatomal Herpes Zoster in December, 1992; and, on several occasions during 1993 and 1994 for Diarrhoea and Vomiting. She had symmetrical polyarthrititis affecting the ankles, Tarsal joints, and all small joints of the Hands and Feet with sausaging of all digits. There was gross oedema of involved limbs but, despite the appearance, there was only moderate tenderness and she could walk without difficulty. Indomethacin 25mg TID led to a dramatic resolution of symptoms and signs. The pain and swelling had resolved completely by the end of the first week of treatment. The arthritis remained in

Remission six months later when she was admitted for yet another episode of diarrhoea with vomiting. The wasting syndrome had set in by this time and she died in October, 1995.

In addition to the six patients with chronic diarrhoea predating arthritis, another thirty-two patients (17 USA and 15 ReA) developed chronic diarrhoea in the course of follow-up. Two of these patients developed chronic diarrhoea after Arthritis had gone into remission. At the onset of chronic diarrhoea many of the patients with active disease experienced recurring exacerbations of joint symptoms with each recurrence of diarrhoea. But thereafter, there was a progressive reduction in signs of joint and extra-articular inflammation, burning out completely in eleven patients. In another five patients, arthralgia and bone pains without evidence of synovitis or bone tenderness became the dominant musculoskeletal affliction. In an additional four patients recurring enthesitis including chondritis continued to be experienced.

F3: CHANGE IN HIV CLINICAL STAGE DURING FOLLOW-UP:

Table XI shows the changes in HIV clinical stage recorded in patients belonging to the different diagnostic categories of seronegative arthritis.

There were six patients from the "Arthritis Alone" (AA) group; Ten from the Reactive Arthritis (ReA) group; and seventeen from the Undifferentiated Spondylarthropathy (USA) group.

TABLE XI: CHANGE IN HIV CLINICAL STAGE DURING FOLLOW-UP

CHANGE IN HIV CLINICAL STAGE	AA	R & A (ALL REITER'S DISEASE)	U.S.A	TOTAL (MEAN DISEASE DURATION)
STAGE 1 TO 2	02	00	04	06 (35.8 MONTHS)
STAGE 1 TO 3	01	05	07	13 (29.9 MONTHS)
STAGE 1 TO 4	00	01	01	02 (22.0 MONTHS)
STAGE 2 TO 3	00	01	00	01 (12.0 MONTHS)
STAGE 2 TO 4	--	--	--	--
STAGE 3 TO 4	03	03	05	11 (33.2 MONTHS)
TOTAL (MEAN DISEASE DURATION)	06 (53.2 MONTHS)	10 (27.0 MONTHS)	17 (26.0 MONTHS)	33 (31.2 MONTHS)

The mean duration of disease is shown against the Marginal and Column totals. These patients were followed up for an average of 10.9 months (range 2 - 22 months). Thirteen patients died (9 males and 4 females) after an average duration of disease of 36.8 months (range 5 - 98 months) and a mean follow-up period of 7.1 months (range 2 - 16 months). The proportion of patients changing clinical stage in the three diagnostic categories (i.e "AA", ReA, and USA), are comparable (10 per cent of 59, 12 per cent of 86 and 17 per cent of 98, respectively). However, there is a notable difference in the mean duration of disease in the "AA" group compared to that in the other diagnostic groups. Whereas the average duration of disease in the patients registering a change in HIV clinical stage was the same at 27 and 26 months in the ReA and USA groups, respectively, the duration of disease in patients in the "AA" group was twice as long at 53.2 months.

This observation suggests more rapid deterioration of HIV clinical stage in ReA and USA than in "AA". This seems a logical consequence in view of the observation that ReA and USA patients were in a more advanced HIV clinical stage at entry to the study. However, differences in disease activity may also play a role.

Available evidence shows ReA and USA to be more severe clinically than AA with:

- (i) MORE JOINT INVOLVEMENT (9.2 joints in ReA and 10.1 joints in USA compared to 5.7 joints in AA);

- (ii) MORE PERSISTENT DISEASE (8 per cent of AA patients compared to 20 per cent of ReA and 26 per cent of USA patients had current disease of more than 6 months duration at first contact) and,
- (iii) LESS FAVOURABLE RESPONSE TO NSAID THERAPY (Remission or Improvement coming after 25.7 weeks of treatment in AA patients compared to 30.6 weeks in ReA and 40.3 weeks in USA patients).

To summarise, four facts emerge from these observations of HIV - positive patients, VIZ:

- (i) Patients in the clinical category "AA" are generally in an earlier stage of HIV infection. They are however, not a homogeneous group, a sizeable proportion of them manifesting spondylarthropathic features during follow-up. Twenty-six patients developed enthesopathies in the course of follow-up and were Re-classified under USA. Twenty-four of these 26 patients were tested for HIV and they were all HIV - positive. There was however, no demonstrable difference in the HIV clinical status of these patients compared to those that remained AA at the time of the change.
- (ii) ReA and USA are comparatively more aggressive clinically with a much slower rate of response to non-steroidal therapy.
- (iii) The HIV Clinical state may deteriorate more rapidly in patients with ReA and USA.

- (iv) Spontaneous amelioration of symptoms may occur with worsening HIV clinical stage, thus improving responsiveness to non-steroidals.

PART II : OTHER CONDITIONS

A : INFLAMMATORY MYOSITIS

Inflammatory Myositis was the second most common condition found. There were a total of twenty-four patients (20 males, and 4 females), with a mean age of 36 years (range 21 - 55 years).

The onset was acute with fever in nine patients but it was more insidious in the remaining fifteen patients in whom the symptoms were those of increasing exercise related pain and undue fatigability in the affected muscles. Polyarthralgia accompanied the disease in eleven patients.

Examination revealed tender muscles which were often swollen. Girdle muscles were often involved while calf, thigh and paraspinal muscles were involved occasionally.

The Erythrocyte Sedimentation rate (westergren) was invariably raised in all patients. Four of six patients had raised creatinine kinase while nine of eleven patients had raised Asparatate Aminotransferase (AST).

Twenty-three patients were tested for HIV, and seventeen (74 per cent) were seropositive.

The HIV Clinical stages (WHO) in these patients were as follows; STAGE 1: eleven patients; STAGE 2: one patient; STAGE 3: three patients; and, STAGE 4: two patients.

B: RHEUMATOID ARTHRITIS AND PALINDROMIC RHEUMATISM

There were twenty-one patients with Rheumatoid arthritis (4 males and 17 females). They all satisfied the diagnostic criteria of the American Rheumatism Association (ARA) for Rheumatoid arthritis (60). Twelve patients had classical disease and the other nine patients had definite disease.

The latex test for Rheumatoid factor was positive in fifteen patients. Erosive disease was present in nine patients, two of whom were cases of Juvenile Rheumatoid arthritis (age 17 years and 24 years, both females).

Episcleritis was present in the surviving eye of a 60 year old woman with disease of more than 10 years' duration who had had disease in the other eye 3 years previously leading to perforation and loss of vision.

Subcutaneous nodules were found in one patient, a 60 year old woman. She was Rheumatoid factor positive.

Sjogren's syndrome was present in a 55 year old Rheumatoid factor positive woman.

The patients were generally much older than those in the diagnostic groups considered so far. The mean age was 51.1 years (range 17 - 80 years). None of thirteen patients tested seropositive for HIV.

Five patients had PALINDROMIC RHEUMATISM. These patients all had a typical history characterised by recurrent, acute, but self-limiting attacks of arthritis. There was one man and four females. The man (an Indian) had a sister with Rheumatoid Arthritis. He was Rheumatoid factor positive. One of the female patients was also Rheumatoid factor

positive. The mean age was 47 years.

C : GOUT: There were twenty-one patients with gout (19 males and 2 females) with a mean age of 53.7 years (range 23 - 78 years).

Sixteen patients had chronic polyarticular disease, ten of whom had tophi (around the ear lobes in two patients). Six patients of this group had X-Ray changes with typical "punched - out" erosions.

In the other five patients, there was a typical history of recurring podagranplus demonstrable hyperuricaemia in between attacks.

In the two female patients gout was associated with diuretic use for hypertension.

These patients were also obese. Three men had associated medical diseases. The first one a 60 year old man with polyarticular and tophaceous disease was obese and had hypertension. The other two had Diabetes Mellitus in addition to hypertension. One of these later two patients who was HIV - positive and obese demonstrated a marked reduction in the frequency and severity of attacks of gout and remission of diabetes as he shed weight due to the HIV infection.

In two male patients (ages 23 and 43 years) gout developed in their late teens. The 23 year old patient had family history of the disease affecting male members. His elder brother had also had disease starting in the late teens and he died at age twenty-five. There had also been two

maternal uncles that ended the same way as his elder brother. This young man had severe poly-to-phaceous disease and huge tissue and joint deposits of amorphous porridge-like uric acid. Many of these had broken down, discharging the material. Acute renal failure supervened and he died. Heterozygous Lesch-Nyhan syndrome was suspected and there was a demonstrable increase in uric acid excretion with a uric acid/creatinine ration of 2. Technical difficulties could not permit confirmation of the diagnosis as we could not measure erythrocyte Hypoxanthine - guanine phosphoribosyl transferase (HG PRT - ase).

D: JUVENILE CHRONIC ARTHRITIS (JCA): Of the 14 patients with JCA, 8 had polyarticular disease. There were two female patients with still's disease both of whom had still's rash.

One patient, an 18 year old male had spondylarthropathic disease with ankylosis of tarsal joints and unilateral radiological sacroiliitis.

No ocular complications were recorded.

E: OSTEOARTHRITIS AND SEPTIC ARTHRITIS: Nine patients with Osteoarthritis and five with septic arthritis were seen. These numbers are not a true reflection of the prevalence of these conditions as they are normally referred to Orthopedic or General Surgeons. The ones that turn up at the arthritis clinic, therefor, represent improperly filtered patients.

Of the patients with Osteoarthritis, six had knee joint

disease - unilateral in four and bilateral in two patients who also had spinal disease. One male patient had disease of an ankle joint related to an old soccer injury. Two patients (1 male and 1 female) had primary generalised Osteoarthritis with *herbedens* nodes.

The mean age of the osteoarthritis patients was 59.1 years (range 50 - 70 years). There were three male and six female patients. None of seven patients were HIV - positive.

The five patients with septic arthritis included two children. Two adult patients were HIV - seropositive.

F: SOFT TISSUE LESIONS: The lesions in the eight patients with soft tissue Rheumatism included DEQUERVAIN'S TENOSYNOVITIS in four female patients; CARPAL TUNNEL SYNDROME in 2 female patients; An entrapment neuropathy in a 70 year old man and shoulder capsulitis in a 38 year old man who was the only HIV - positive patient in this group.

G: NEISSERIAL REACTIVE ARTHRITIS AND POLYARTHRALGIA:

Four patients had acute sterile polyarthrititis in association with Meningococcal Meningitis. There were two males and two females. All were HIV - seropositive. Only one of them had stigmata of HIV infection - a 24 year old female with generalised Lymphadenopathy and oral candidosis.

Joint inflammation in these patients characteristically resolved promptly upon starting non-steroidal anti-inflammatory drugs - all symptoms disappearing within 1 week of therapy in all four patients.

Five patients had non-specific polyarthralgia. All were male patients and all four patients that were tested were HIV seropositive. The clinical presentation fitted that of the PAINFUL ARTICULAR SYNDROME as described by Berman et al (3). All patients were afflicted by recurring episodes of joint pain of short duration but without objective evidence of synovitis. The pains were most frequently described in the shoulder, wrists, knees and small joints of the hands. All four patients were in WHD Clinical stage 1 (2 asymptomatic and 2 with PGL).

H: MISCELLANEOUS: Conditions in the miscellaneous category were:-

- (i) OSTEOPOROSIS (3 patients none of whom tested positive for HIV antibodies). There were two female patients and one male patient. The male patient, a Coloured man of 82 years of age had severe disease with compression fractures of vertebral bones as well as pathological fractures of his pelvis and femora. both females were postmenopausal and were afflicted by chronic back pain and polyarthralgia and bone pain. They had no stigmata suggestive malignant disease and skeletal radiological survey and gynecological examination were negative in this regard.
- (ii) BONE TUMOUR (3 patients; all male). Two were tested for HIV and they were both HIV - negative. Two patients had osteosarcoma while one had a chondroma.

- (iii) There were two patients each with Herpes Zoster arthritis, Avascular Necrosis and Tuberculous arthritis. All these six patients were HIV - seropositive.
- (iv) SYSTEMIC LUPUS ERYTHEMATOSUS (SLE): There were two female patients with S.L.E. Both were HIV - seronegative.
- (v) Finally, there were two patients each with Rheumatic Fever and Intervertebral disc prolapse, and one patient with sickle cell arthritis.

One of the Rheumatic Fever patients was a 21 year old man with Rheumatic heart disease of many years' standing who was referred to the U.T.H. from a Rural District Hospital for superimposed acute Rheumatic Fever.

One of the two patients with disc prolapse was a 34 year old man with Diabetes Mellitus. He was HIV - seropositive.

TABLE XII: CASES OF DYSENTERY AND ARTHRITIS AS PROPORTIONS OF THE TOTAL ADMISSIONS FOR THE YEARS 1985 - 1994.

YEAR	TOTAL ADMISSIONS (ADULT PATIENT)	DYSENTERY ADMISSIONS AS % OF TOTAL	ARTHRITIS ADMISSIONS AS % OF TOTAL
1985	62, 954	0.08	0.19
1986	61,631	0.07	0.24
1987	61,251	0.11	0.32
1988	61,251	0.16	0.38
1989	56,186	0.06	0.37
1990	58,459	0.05	0.32
1991	56,930	2.84	0.36
1992	66,197	3.52	0.48
1993	60,210	1.58	0.44
1994	61,207	1.15	0.38

SERONEGATIVE ARTHRITIS: SULPHASALAZINE THERAPY.

In order to investigate the safety and efficacy of sulphasalazine, fourteen patients were entered into an open study.

There were Ten males and Four females aged 28 - 47 years. The mean disease duration was 3 years and current active disease duration of 8 months. The clinical diagnoses were undifferentiated spondylarthropathy in 7 patients and Reactive Arthritis in the other 7 patients.

Thirteen patients completed 3 months therapy and eleven patients completed 6 months treatment. There was one withdrawal at one month for dizziness and one death at 3 months for infective endocarditis in a patient with Aortic Regurgitation. One patient who had become asymptomatic at the end of 3 months treatment was lost to follow-up.

There was gratifying response in nine of the eleven patients that took treatment for 6 months. There was a progressive reduction in pain, tender and swollen joints, as well as in both the patients and physician's global assessment of disease activity. One of the two poor responses was probably due to non compliance.

The majority of the patients took 1.5gm of Sulphasalazine daily. Improvement was most marked during the first 1 - 3 months (Tables XIII and XIV. There was no case of renal, hepatic or Bone Marrow toxicity. The mean Haemoglobin concentration rose from $9.5 \pm 0.52 \text{ g/dl}$ at the start of therapy to $10.1 \pm 0.6 \text{ g/dl}$ at 3 months and to $10.50 \pm 0.69 \text{ g/dl}$ at 6 months. There was a progressive fall in the mean

TABLE XIII: SULPHASALAZINE TRIAL: CLINICAL RESULTS

TIME	PAIN SCORE (VAS) (MEAN $\pm$ S.E)	JOINT COUNTS (28 JOINT COUNT)		PATIENT'S GLOBAL ASSESSMENT (VAS)	PHYSICIAN GLOBAL ASSESSMENT (5 POINT SCORE)
		TENDER JOINTS	SWOLLEN JOINTS		
START	6.1 $\pm$ 0.5	16.6 $\pm$ 2.0	6.4 $\pm$ 1.5	6.2 $\pm$ 0.5	3.4 $\pm$ 0.14
3MONTHS	3.4 $\pm$ 0.6	5.4 $\pm$ 2.1	3.0 $\pm$ 2	3.5 $\pm$ 0.68	2.0 $\pm$ 0.24
6MONTHS	2.5 $\pm$ 0.6	2.8 $\pm$ 1.9	0.4 $\pm$ 0.4	2.6 $\pm$ 0.68	1.5 $\pm$ 0.24

VAS = VISUAL ANALOGUE SCALE

TABLE XIV: SULPHALAZINE TRIAL: LABORATORY RESULTS.

TIME	Hb (g/dl)	ESR (mm/hr)	WBC ($10^3/\text{mm}^3$)	LYPHOCYTE %	LYMPHOXYTE (DIFFERENTI AL CONT.)	PLATELETS ($\times 10^3/\text{MM}^3$)
START	9.5 ± 0.52	114 ± 5.8	6.2 ± 0.34	31 ± 1.7	1876 ± 97	401 ± 50
3MONTHS	10.1 ± 0.6	97 ± 7.5	5.9 ± 0.54	33 ± 3.0	1823 ± 99	292 ± 22
6MONTHS	10.5 ± 0.69	89 ± 11.7	5.7 ± 0.79	35 ± 4.2	1849 ± 263	286 ± 42

Erythrocyte sedimentation rate (ESR) and the mean platelet count.

CONCLUSION: These results confirm earlier anecdotal reports of the beneficial effect of Sulphasalazine in HIV - related spondylarthropathy (46, 47). Clearly, controlled clinical trials of the drugs are indicated by these encouraging results.

DISCUSSION

This study has defined the relative frequency of inflammatory rheumatic disorders in patients attending the University Teaching Hospital, Lusaka.

Selection is not likely to have affected the results since most patients attend the hospitals Out-Patients Filter and/or Casualty Departments as self referrals. Most of these patients plus those discharged from the hospital's In-Patient services were referred to the arthritis clinic for onward care and/or further evaluation. The waiting period for new appointments to this clinic is 2 - 3 weeks and 90 per cent of patients kept this appointment.

The spectrum of conditions that emerges, therefore, must be representative of the true picture for Lusaka. The identification of patients with Rheumatoid Arthritis, Gout and Juvenile Chronic Arthritis reflects the growing awareness of these disorders in indigenous black populations of sub-Saharan Africa (62, 63).

The HIV - seroprevalence in the general outpatient adult population at the hospital is not known for sure although it is believed to lie around 50 per cent. In a sentinel survey of the HIV - infection load on the Internal Medicine In-Patient service of the U.T.H., in the later part of 1992, a Seroprevalence of 70 per cent was found (personal communication). These seroprevalences are contrasted with the estimated population HIV - seroprevalence of around 30 per cent.

The HIV - seroprevalence of 75 per cent found among patients with musculoskeletal disorders is high and compares to that in the population of medical in patients that are a more highly selected group owing to admission criteria which tend to favour admission of very ill or terminally ill patients. The contribution made by seronegative arthritis to this high HIV - seroprevalence is obviously great and the seroprevalence of 84 per cent in this population of patients is significantly higher than that found in Medical In-Patients or that found in Kasongo's series (30). This data confirms the existence of spondylarthropathies in this population of mostly Indigenous black Zambians. The Clinical and Radiographic features of these disorders are similar to those described in HLA-B27 positive caucasians. This, obviously raises the question of Pathogenetic Mechanism since previous studies have not shown an association with HLA - B27 in the African Disease (28). Cross-Reacting antigens may play a role. Stein and Davis (61) found B-7 cross reactive antigens in six (46 per cent) of 13 HIV-infected Zimbabwean patients with Reiter's Disease. But this possibility is unlikely to be the only explanation and does not explain the recent unprecedented rise in the prevalence of Spondylarthropathies in a population that has relatively been unaffected by these disorders. A direct role by HIV in the pathogenesis of these spondylarthropathies is unlikely as is made obvious by epidemiologic studies from America (24, 25, 26) which have

demonstrated no association between HIV infection and Rheumatic diseases. However, the results of this study, and those of others from Africa (4, 29, 30) tend to confirm the view that HIV infection predisposes to spondylarthropathies and alters the clinical course of the disease. To explain the wide region to region variation in the prevalence of HIV-associated spondylarthropathic disease, additional environmental factors must be postulated.

In Zambia, there were widespread epidemics of *Shigella* dysentery at the beginning of the 1990's. Currently, the disease is endemic in many parts of the Republic.

To investigate the influence of the *Shigella* epidemic on the prevalence of acute arthritis at the U.T.H., we sought to review Out-Patient attendances for these conditions over a Ten year period starting from January, 1985 and ending December, 1994. This was not feasible, however, since Out-Patient data on Dysentery are recorded under the broad group of Diarrhoeas, whereas arthritic problems are recorded under the broad group of musculoskeletal problems.

We were, however, able to review records of In-Patient cases of the two conditions. Between 1985 and 1990, cases of Dysentery averaged 54 per year (range 29 - 96) while cases of acute arthritis averaged 181 per year over the same period. There was no correlation in the way the numbers of the two conditions fluctuated during those six years.

In 1991, there was a 30 - fold rise in admissions for Dysentery (total of 1,617 cases). This figures rose 1.4

times in 1992 to 2330 cases. Thereafter, the numbers dropped to 952 in 1993 and to 705 in 1994. Cases of arthritis during the 1991 to 1994 period correlated positively with the rise and fall in the number of cases of Dysentery with a correlation coefficient of 0.396.

Table XII shows cases of Dysentery and of arthritis as percentages of the total admissions for each year from 1985 to 1994. Although the rise in the numbers of arthritis was NOT as dramatic as that for Dysentery, the emerging pattern in the four years suggests a contribution by Dysentery to the prevalence of arthritis.

In this study, up to 75 per cent of patients with reactive arthritis or about a quarter of all patients with spondylarthropathic disease, had Dysentery as the preceding trigger.

The inevitable question is: "Are HIV - infected individuals more susceptible to post-dysenteric reactive arthritis than HIV - negative ones?"

The answer to this question seems to be a NO. There was no demonstrable difference in the number of HIV - positive and HIV - negative patients reporting a preceding bout of Dysentery (63 of 243 HIV - positive compared to 11 of 47 HIV - negative patients ODDS RATIO = 1.15; 95% C.I. = 0.52 - 2.55; P = 0.72).

Although Kasongo concluded that Dysentery occurred more frequently in HIV - negative than in HIV - positive patients (30), re-analysis of his data shows his finding to be

consistent with the finding of this study. He observed fifteen post-dysenteric cases among 65 HIV-positive patients and 18 cases among 54 HIV-negative patients. The χ^2 with Yate's correction = 1.0787; ODDS RATIO = 0.6; P = 0.3. The difference he observed could, therefore, have arisen by chance.

Other trigger factors are obviously operative. Urogenital infections appear to play a relatively minor role. However, systematic studies, for example, for chlamydia were not carried out owing to technical difficulties.

The clinical features of spondylarthropathic disease observed in the patients in this series resembles the classical disease described in HLA - B27 positive patients in a number of ways including:-

- * The age structure of patients affected (young adults).
- * Prevalence of enthesopathies i.e 51 per cent (53).
- * Predilection for the weight bearing joints of the lower limbs and the MTP joints.
- * Radiologic features of MTP joint erosion, enthesitis and periostitis.
- * a number of extra-articular features.

Furthermore, the disease in HIV-positive patients shares most of the attributes noted in HIV-Infected, HLA - B27 positive caucasians (1).

These included:-

- * Persistent unremitting disease.
- * Progressive, frequently relapsing disease.

- * Poor response to Non-steroidal anti-inflammatory drugs.
- * Erosive disease.
- * Sustained Enthesopathies.

Previous studies have emphasised the oligoarticular nature of the HIV-related disease. We have noted one more point of difference from the disease in HIV-negative patients. This is that the disease in HIV-positive patients, being of an additive nature, does eventually become polyarticular either in the current episode or in a subsequent relapse. The combination of polyarticular disease and Enthesitis is virtually diagnostic of HIV-associated disease.

Since the majority of patients may be HLA-B27 negative as shown by previous studies (50,61,64), it seems plausible to postulate that the HIV-infected state and the possession of HLA antigen B27 share a similar predisposition to developing an abnormal immunological reaction following appropriate stimulation leading to the development of arthritis. A defective handling of an infectious factor, for example, possibly starts the train of events that lead to arthritis and other lesions.

Previous studies have shown the significant role played by suppressor cells in Rodents with adjuvant arthritis (65) and with autoimmune disease (66).

Antigen specific suppressor cell activity appears crucial in preventing autoimmune phenomena in the rodent model.

Failure to induce such suppressor T-Cell activity results in arthritis and autoimmunity disease.

Protean immunological abnormalities occur in HIV-infected individuals including functional abnormalities of T-Lymphocytes and Macrophages. Helper T-cell and macrophage function is crucial for the induction of T-Suppressor cell activity. It is conceivable that such suppressor T-Cell activation fails in HIV-infected persons following challenge with certain types of antigen.

There are several other ways in which the altered immunological state in HIV-infected persons might predispose to autoimmune disease and arthritis. Winchester et al (1) and Solomon et al (21) have postulated several ways in which HIV might contribute to the emergence of reactive arthritis. Firstly, the early expansion of the CD8 - positive cells that occurs in HIV-infection might favour the emergence of autoreactive CD8 - positive cells. Secondly, it is postulated that the immunodeficient state might impair the ability to eliminate infective microbial organisms leading to microbial persistence. Thirdly, there may be an upregulation of class I HLA expression by elevated levels of cytokines, a state which enhances the likelihood of effective antigen presentation.

Autoreactivity to heat shock proteins (hsps) is another possible pathogenic mechanism. Heat shock proteins are highly conserved in evolution and hsps of Bacteria and other infectious organisms share structural homology with human hsps. Heat shock proteins on infecting organisms constitute the major target of the host's immune response and

antibodies and T-Cells against hsp's of *Mycobacteria*, *Plasmodium falciparum* and *Schistosoma mansoni* have been detected in individuals infected with these organisms (68, 69).

Autoreactivity to HSPs appears to occur on a background of a concomitantly existing enhanced expression of the host's hsp's (70). This phenomenon can be brought about by many factors including viral infections (71).

Direct evidence of hsp's causing autoimmune disease is provided by cases of adjuvant arthritis in Rats which, following injection with an extract of heatkilled *Mycobacterium tuberculosis* in Freud's complete adjuvant, develop T-cells specifically reacting with the *Mycobacterium* HSP 65 protein. Such T-cells have been shown to cause disease when transferred to irradiated rats that have not been previously exposed to *Mycobacterium tuberculosis* (68,69,70).

This scheme provides possible answers to the apparent paradox of emergence of spondylarthropathies in a population that lacks genetic predisposition to the disorders. Region to region variation in the prevalence of these disorders would be explainable under this scheme on the basis of differences in the prevalence of additional environmental cofactors or on the basis of the modification of the HIV-induced immunological abnormalities by the use of drugs such as AZT.

Finally, the clinical stage of the HIV-infection may also be

an important factor in determining prevalence of these disorders. Since the arthritic problems start early in the course of HIV infection, their prevalence will vary according to the pool of HIV infected individuals with early disease. Part of the explanation to the high prevalence of arthritis in Africa may be the fact that the incidence of new HIV infections remains high. On the other hand, the incidence of new HIV infections in the West is low and declining so that the HIV infected population pool consists of more individuals in the later stages of HIV infection. In this study a reduction in disease activity has been noted as patients descended the clinical stages of HIV infection and developed chronic diarrhoea and/or the wasting syndrome. Additional circumstantial evidence that spondyarthropathies rarely occur for the first time in the later stages of HIV infection and in full-blown AIDS is provided by clinical observations on the In-Patient wards of this hospital. Over the past two years, thousands of encounters with patients with AIDS wasting syndrome and other AIDS - defining disorders have only turned up a handful of patients with spondylarthropathic disease - the six patients reported under the chronic diarrhoea section.

This observation strengthens the view that spondylarthropathies may be mediated and sustained by an exhaustible factor in HIV-infected patients.

CONCLUSIONS.

1. SPONDYLARTHROPATHIES are the most prevalent Rheumatic disorders occurring in association with HIV-infection in Lusaka, Zambia. These share many clinical and Radiological features with the disease in HLA - B27 positive individuals.
2. The association with HIV-infection is overwhelming. This, together with the demonstrable difference in clinical behaviour from the disease in HIV-negative patients strengthens the view that the Human Immunodeficiency Virus predisposes to spondylarthropathic disease.
3. Additional enviromental factors acting on the background of the altered immunological state induced by HIV infection are the likely triggers of spondylarthropathic disease.
4. Non-steroidal anti-inflammatory drug therapy will be needed by the majority of HIV-positive patients on an indefinate basis, often in maximal doses. It is gratifying that when taken correctly - soon after meals - Indomethacine is NOT associated with an undue rate of gastrointestinal complications.
5. Enthesitis and Polyarticular involvement are distinctive features of the HIV - associated disease. Enthesitis and small joint involvement are prognostic markers for severity and persistance.
6. Disease activity generally reduces as the Immunological

state of the patient worsens and AIDS - defining features set in. Paroxysms of arthralgia and bone pain and recurring milder episodes of enthesitis, however, may continue to haunt the patient even in these later stages of HIV-infection.

7. Shigella dysentery while contributing to the problem of Reactive Arthritis, does not seem to predispose HIV - infected individuals specifically. Neither does it appear to be the only operative predisposing trigger factor to the disease as seen in Lusaka.
8. Sulphasalazine appears safe and efficacious in HIV - associated spondylarthropathy with prompt early response. This is particularly encouraging as many patients may have the promise of early return to normal or near normal activity within a few weeks or months of treatment.

RECOMMENDATIONS

1. Whereas in the past, emphasis has been placed on the likelihood of cross reactivity and molecular mimicry between HLA - B27 and Microbiological components to explain the pathogenesis of spondylarthropathies, the weight of the current evidence suggests that the ability to mount an appropriate immunological response to an immunological challenge may be the final common pathway. Genetic factors as well as on-going events within the individual's immune system may predispose to mounting an aberrant immunological response following

appropriate challenge. Therefore, a host of factors may interact to determine those who develop spondylarthropathies following challenge with an environmental trigger such as shigella infection, for example.

Future studies evaluating the state of the cellular and humoral components of the Immune system in HIV infected persons with arthritis are indicated. In this regard, quantitative and functional abnormalities of CD4 positive and CD8 positive T-cells as well as immunoglobulin and cytokine profiles in such patients need studying. Furthermore, correlation studies of the state of these immune components with the natural history of arthritis could identify the most important elements that initiate and sustain HIV-associated arthritis. We stand to gain a great deal of knowledge about the pathogenesis of autoimmune disease from such studies.

Studies searching for concomitant infections or evidence of bacterial persistence are also indicated. The gut seems to be most appropriate place to start the search from. Endoscopic studies accompanied by appropriate sampling of tissue and microbiological specimens should characterise the gut lesion(s) in patients with ulcerative colitis-like symptoms as well as clarify the issue whether such symptoms are infection-driven or otherwise.

2. The results of this study should leave very little doubt if any about the association between HIV infection and certain manifestations of seronegative arthritis. The HIV associations with duration of disease, episode number, specific seronegative arthritis syndrome, pattern of joint involvement and with enthesitis and other extra-articular lesions should help Clinicians dealing with such patients identify those with the greatest odds of being HIV infected. More importantly, these facts could be incorporated into the information-to-patients package for purposes of patient education as well for counselling purposes. The likelihood of HIV infection could be put into context very easily on the basis of data in this thesis, depending on the type and clinical characteristics of the arthritis syndrome in the individual patient. A common question patients with arthritis ask is, what the cause for their problem could be? An unhurried explanation about the many types of arthritic syndromes (Rheumatoid arthritis, gout, trauma, Reactive arthritis, etc) followed by an explanation about the association between gut and urogenital infections (with examples) and seronegative arthritis (which is the point of discussion here), ending with an explanation about the observation in recent years of a high association between HIV infection and seronegative arthritis (of the order of 80% in Zambia) will often elicit a voluntary

request for an HIV test or for information about how to protect their spouse in case they are actually HIV-infected.

The information about HIV associations must be handed very delicately with the patient, limiting oneself to generalisations and emphasising the point that statistics tell facts about large groups of people (in the case of serogative arthritis, current facts say that about 80 out of 100 persons with this condition may be HIV-infected) and that they (statistics) have limited applicability to the individual about whom the facts might be that he/she has HIV infection or does not. Therefore, one can point out to ones patients that the only way to tell for sure which side they fall (HIV - infected or not) would be through having an HIV test. This must be communicated in a non-prompting manner, leaving the final choice to the patient.

3. The likely out come of the arthritis problem must be put into context for the patient at the earliest opportunity. Generally, the patient's disease will behave in one of three ways, Viz:
 - (i) a one off attack, resolving within a few weeks or months.
 - (ii) persistent disease lasting many months or even years and,
 - (iii) relapsing disease with varying durations between episodes of active disease. It must be pointed

out to the patient that time only will tell which way their disease will behave, but the opportunity to consolidate this fact must never be lost by making appropriate reference to previous behaviour of the individual patient's disease especially for those with disease of longer duration or with disease recurrence at first contact. This creates the background against which to discuss the need for regular and uninterrupted medication. The message to emphasise is that medications will have to be taken for as long as symptoms last.

Presently, Indomethacin and Iboprufen have the greatest prospects for long term availability. They are affordable and provide acceptable symptomatic relief for the majority of patients when used in appropriate anti-inflammatory doses. These non-steroidals should be used at the lowest doses which induce and sustain symptomatic relief. For most patients with severe disease, Indomethacin 50mg TDS or Iboprufen 600mg TDS appear to be the appropriated starting doses. These must be taken soon after meals to lessen the likelihood of non-steroidal induced gastropathy.

4. Transient episodes of arthralgia were reported by many patients in the course of their disease. These occurred independently of relapse or exacerbations in both HIV -

positive and HIV - negative individuals with spondylarthropathies. This is a recognised behaviour of spondylarthropathies. However, the group of patients with "Painfull Articular syndrome" (PAS) are interesting and need further study.

All the four HIV-positive patients reported in this thesis (part 2G) were in early HIV clinical stages. In our experience, transient (or fleeting) pains in the joints and soft tissues especially of the lower limbs are very common in HIV infected patients in the later stages of HIV infection. In a preliminary survey of 50 consecutive male patients with chronic diarrhoea admitted onto our unit's In-Patient ward in the first quarter of 1995, 38 reported pain in the distal leg and/or foot. The majority of these patients had painful sensory neuropathy while the rest reported recurring paroxysms of moderate to severe pain about the ankle joints, the foot and distal leg but exhibited no abnormality on examination, (unpublished observations). The inervitable question raised by these observations is whether there is a connection between painful articular syndrome (PAS) and sensory neuropathy. Does "PAS" represent an earlier stage of painful sensory neuropathy? What is the role of Nutrient deficiencies, toxic factors and/or infective agents? Studies evaluating the integrity of the peripheral nervous system as well as studies seeking the role for nutrient

and other causes for neuropathy should clarify the role of the nervous system, if any in painful articular syndrome.

5. Data in this thesis suggests that more severe and persistent disease in HIV infected patients does accelerate the progression of HIV infection down the clinical stages. We have also demonstrated that the disease activity (arthritis) reduces in later stages of HIV infection. These facts raise important issues about therapy for arthritis in such patients.

Firstly, non-steroidal antiinflammatory drugs alone seem inadequate to halt the arthritic process and hence the deterioration in the HIV Clinical stage. Disease modifying anti-rheumatic drugs (DMARDS), started early in the disease could probably make the difference.

Sulphasalazine appears to be safe and effective, inducing a gratifying amelioration of symptoms and signs within the first 4 weeks of starting treatment.

Although we can not make a claim on the basis of our data for Sulphasalazine to delay the progression of HIV infection, its prompt induction of response is

remarkable. It means that patients taking this drug

have the favourable prospect of improving in their

functional status and of becoming asymptomatic more

quickly. In the face of evidence from elsewhere that

some DMARDS such as Azathioprine and Methotrexate may

have a deleterious effect on the HIV clinical state

(1,21), Sulphasalazine appears a reasonable alternative for our patients with severe arthritis and HIV infection.

Secondly, the spontaneous amelioration of arthritis symptoms noted in the later stages of HIV infection makes it possible to treat patients on much lower doses of non-steroidals or even with simple analgesics.

Generally, this means that one has little prospect of having to use high dose non-steroidals in the context of severe immunosuppression with its attendant propensity to be associated with diarrhoea and dehydration which would enhance the likelihood of non-steroidal renal toxicity.

6. It is remarkable that we have been able to identify so many patients with juvenile chronic Arthritis, rheumatoid arthritis and gout. Extension studies are needed to document and characterise these conditions which have until recently also been rarely reported in Africans in Africa.

Electromyographic and muscle biopsy studies are needed to characterise the pathology in those with Myositis.

7. Finally, owing to limited availability of laboratory facilities for the investigation of patients with arthritis locally, collaboration with a rheumatology laboratory elsewhere on certain aspects of future study would be beneficial. This would enable a comprehensive search for the numerous infective agents capable,

directly or indirectly, of causing arthritis, or to examine the association of HIV-associated arthritis with HLA B27 by tissue typing.

REFERENCES:

1. Winchester R, Bernstein DH, Fischer HD, Enlow R, Solomn G. The Co-occurrence of Reiter's Syndrome and Acquired Immunodeficiency. *Ann Intern Med.* 1987; 106:19-26.
2. Foster SM, Seifert MH, Keat AC, et al.. Inflammatory joint Disease and Human Immunodeficiency Virus Infection. *Br. Med J. (Clin. Res).* 1988; 296:1625-27.
3. Berman A, Espinoza LR, Diaz JD, et al. Rheumatic manifestations of Human Immunodeficiency Virus Infection *Am J. Med.* 1988; 85:59-64.
4. Davis P, Stein M, Latif A, Emmanuel J. HIV and Polyarthrititis (Letter). *Lancet.* 1988; 1:936.
5. Buskila D, Gladman DD, Langevitz P, Bookman AAM, Fanning M, and salit IE. Rheumatologic Manifestations of Infection with the Human Immunodeficiency Virus (HIV). *Clin. Experimental Rheumatol* 1990; 8:567-73.
6. Dalakas MC, Pezeshpour GM, Gravel M, Sever JL. Polymyositis Associated with AIDS retrovirus. *JAMA.* 1986; 256: 2381-3.
7. Simpson DM, Bender AN. Human Immunodeficiency Virus-associated Myopathy: Analysis of 11 patients. *Ann Neurol* 1988; 24: 79-84.
8. Stern R, Gold J, Dicarlo EF. Myopathy complicating the Acquired Immune Deficiency Syndrome. *Muscle Nerve* 1987; 10:318-22.
9. Balley RC, Turok DI, Jautmann BP, Singh JK. Myositis and Acquired Immunodeficiency Syndrome. *Human Pathol.*

1987; 18:749-51.

- 10 Calabrese LH, Estes M, Yen-Lieberman et al. Systemic Vasculitis in Association with Human Immunodeficiency Virus infection. *Arthritis Rheum* 1989; 32:569-76.
- 11 Said G, Lacroix C, Andrieu JM, Gaudouen C, Leibowitch J. Necrotising arteritis in patients with Inflammatory Neuropathy and Human Immunodeficiency Virus (HIV-III) infection (abstract). *Neurology*. 1987; 37 (Suppl.1): 176.
- 12 Itescu S, Brancato L, Buxbaum J, Solomon G, Winchester R, Sjogren's Syndrome associated with HIV Infection (abstract). *Arthritis Rheum* 1988; 31 (Suppl): S.35.
- 13 Ulirsch RC, Jaffe ES, Sjogren's Syndrome-like illness associated with the Acquired Immunodeficiency Syndrome related complex. *Hum. Pathol.* 1987; 10:1063-8.
- 14 Cauderc LJ, D'agay MF, Danon F, Harzic M, Brocheriou c, Clauvel JP. Sicca Complex and Infection with Human Immunodeficiency Virus. *Arch Intern Med.* 1987; 147:898-901.
- 15 Davic M, Johnson TM, Rapini RP, Freese T, Breton G, Rios A. Acquired Immunodeficiency Syndrome - associated psoriasis and Reiter's Syndrome. *Arch Dermatol.* 1987; 123: 1622-32.
- 16 Espinoza LR, Berman A, Vasey FB, Cahalin C, Nelson R, German BF: Psoriatic Arthritis and Acquired Immunodeficiency Syndrome. *Arthritis Rheum* 1988; 31:40.
- 17 Brancato LJ, Itescu S, Skovron ML, Mildvan D,

Winchester RJ. Arthritis, psoriasis and related Syndromes associated with HIV infection (abstract). Clin. Res. 1988; 36: 531A.

- 18 Kopelman RH, Zolla-Fazner S. Association of Human Immunodeficiency Virus Infection and Autoimmune Phenomenon. Am. J. Med. 1988; 84: 82-88.
- 19 Bloom EJ, Abrams DI, Rodgers C. Lupus Anticoagulant in the Acquired Immunodeficiency Syndrome. JAMA. 1986; 256:491-3.
- 20 Kaye BR. Rheumatologic manifestations of Infection with Human Immunodeficiency Virus (HIV) Ann Intern Med. 1989; 111:158-67.
- 21 Solomon G, Brancato L, Winchester R. Approach to the Human Immunodeficiency Virus - Positive Patient with a Spondyloarthropathic Disease. Rheum. Dis. North Am 1991; 17(1): 43-58.
- 22 Golsbus J. Rheumatic Disease and AIDS: An interesting but mysterious relationship. Postgrad. Med 1992, 92 (4): 99-110.
- 23 Rowe IF, Forster S.M, Seifert M.H, et al. Rheumatological Lesions in Individuals with the Human Immunodeficiency Virus Infection. Q.J. Med. 1989; 73 (272): 1167-84.
- 24 Clark M, Kinsolving M, Chernoff D: The Prevalence of Arthrititis in two HIV-infected Cohorts (Abstract). Arthritis Rheum 1989; 32 (Suppl 4): 585.
- 25 Solinger AM, Hess EV: Rheumatic Disease and AIDS - is

- the association Real? J. Rheumatol 1993; 20:678-83.
- 26 Hochberg MC, Fox R, Nelson K.E., Saah A: HIV infection is not associated with Reiter's Syndrome: Data from the Johns Hopkins Multicentre AIDS Cohort Study. AIDS 1990; 4: 1149-51.
 - 27 Beral V, Peterman TA, Berkelman RC, Jaffe HW. Kaposi's Sarcoma among persons with AIDS: A sexually Transmitted Infection? Lancet 1990; 335: 123-28.
 - 28 Davis P, Stein M. Human Immunodeficiency Virus - related connective tissue diseases: A Zimbabwean perspective. Rheum Dis Clin North Am 1991; 17(1): 89-97.
 - 29 Jellis JE. The influence of the Human Immunodeficiency Virus on Orthopaedic practice. (Abstract) J. Bone Joint Surg. 1992; 74-B (Suppl II): 202-203.
 - 30 Kasongo Z. A Study of Reactive Arthritis and its Relationship to Human Immunodeficiency Virus Infection. Dissertation for the degree of Master of Medicine (Surgery) of the University of Zambia, Lusaka, Zambia (1993):
 - 31 Winchester R. AIDS and the Rheumatic diseases. Bulletin on the Rheumatic Diseases, 1991; 39(5):1-10.
 - 32 Calin A. Reiter's Syndrome. Med. Clin. North Am. 1977; 61: 365-76.
 - 33 Klemp P, Myers OL, and Dutoit ED. HLA B27 and Ankylosing Spondylitis in African Blacks. Arthritis and Rheumatism 1987; 25:716-17.
 - 34 Van Oosterhout JJ. and Van Der Hoek W. Dysentery

associated with HIV positivity in Rural Zambia. AIDS 1994; 9 (10) : 1512.

- 35 Goodall JWD. Joint swellings in Africans (a review of 90 cases). Central African Journal of Medicine 1956; 2 : 220-21
- 36 Hall L. Polyarthrititis in Nairobi Africans. East African Medical Journal 1963; 40:354 - 58.
- 37 Golfand M. Acute non-specific arthritis in the African Central African Journal of Medicine 1963; 9:276-78.
- 38 Riley MJ. Acute non-specific polyarthrititis. Central African Medical Journal 1976; 22:1-4.
- 39 Greenwood BM. Acute Tropical Polyarthrititis. Quarterly J. Med 1969; 38: 295-306.
- 40 Greenwood EM. Polyarthrititis in Western Nigeria III: Other forms of polyarthrititis. Ann Rheum. Dis. 1970; 29:56 - 63.
- 41 Bagg LR, Hansen Dp, Mutboko IK, and Lewis G. Chronic Polyarthrititis at the Kenyatta National Hospital. East African Medical Journal 1976; 53: 567-72.
- 42 Anon. Acute tropical polyarthropathy: Homogeneous entity or diagnostic scrap-heap? Lancet 1988; 1: 627-28.
- 43 Stein CM and Hanly MG. Acute Tropical Polyarthrititis in Zimbabwe: a prospective search for a gonococcal aetiology. Ann Rheum Dis. 1987; 46:912-14.
- 44 Pike KD, Richens JE, Laurent RM. et al. Arthritis in the highlands of Papua New Guinea. Ann Rheum. Dis.

- 45 ~~Deegan AM~~ 49-53. Viral aetiology of arthritis. Reports on Rheumatic Diseases (Series 2) 1987; Tropical Review: 7.
- 46 Youssef PP, Bertouch JV and Jones P.D. Successful treatment of Human Immunodeficiency Virus - associated Reiter's Syndrome with Sulphasalazine. Arthritis Rheum. 1992; 35 (6): 723.
- 47 Mijiyawa M and David M. Beneficial effect of Sulfasalazine treatment on spondylarthropathy in two HIV-positive males. Revue du Rheumatisme 1993; 60: 437-39.
- 48 Hill AVS, Allsop CEM, Kwiatkowski D. et al. HLA class I typing by PCR: HLA-B27 and an African B27 subtype. Lancet 1991; 337: 640-42.
- 49 Khan MA. B7-Cregg and Ankylosing Spondylitis. Br. J. Rheumatol. 1983; 22 (Suppl 2): 129-33.
- 50 Michael Stein, Paul Davis, Jean Emmanuel and George West. The Spondyloarthropathies in Zimbabwe: A Clinical and Immunogenetic Profile. J. Rheumatol. 1990; 17: 1337-9.
- 51 Harrington WJ, Ucar A, Gill F. et al. Clinical Spectrum of HTLV-1 in south Florida. J. Acq. Immun. Def. & H. Retrovirology 1995; 8(5): 466-73.
- 52 Nishioka K, Maruyama I, Sato K. chronic Inflammatory Arthropathy associated with HTLV-1 (Letter). lancet 1989; 1:441.
- 53 Calin A. Reiter's Syndrome. In Calin A (ed)

- Spondylarthropathies. New York: Grune and Stratton: 1984; PP. 119-149.
- 54 Vasey FB, Espinoza LR: Psoriatic Arthropathy. In Calin A (ed). Spondylarthropathy. New York: Grune and Stratton: 1984; PP 151-185.
- 55 The HSG, Steven MM, Van der Linden SM and Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a comparison of the Rome, N.Y., and Modified N.Y. Criteria in patients with a positive clinical history screening test for ankylosing spondylitis. British J. Rheumatol. 1985; 24: 242-249.
- 56 World Health Organisation. WHO case definition for AIDS Surveillance in Adults and Adolescents. Weekly Epidemiological Record 1994; 69: 273-75.
- 57 Steinbrocker O., Traeger CH., Batterman RC., Therapeutic criteria in Rheumatoid Arthritis. JAMA 1949; 140: 659-62.
- 58 The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum. 1991; 34 (10): 1218-1227.
- 59 Kellgren JH, Jeffey MR, Ball J. The epidemiology of chronic Rheumatism. Volume 1; Oxford: Blackwell Scientific Publication, 1963; appendix 1: PP 324-327.
- 60 Arnett FC, Edworthy SM, Bochs DA, et al. The American Rheumatism Association 1987 Revised Criteria for Classification of rheumatoid arthritis. Arthritis Rheum. 1988; 31:315-24.

- 61 Stein CM, Davis P. Arthritis and Rheumatism 1992; 35(Abstract 12): 536.
- 62 Resenberg ZS, Norman A, Solomon G. Arthritis Associated with HIV Infection: radiographic manifestations. Radiology 1989; 173:171-176.
- 63 Adebajo AO., Epidemiology and community studies: Africa. Clinical Rheumatol. 1995; 9(1): 21-30.
- 64 Mody GM. Rheumatoid arthritis and connective tissue disorders: Sub-Saharan Africa. Clinical Rheumatol 1995; 9(1): 31-44.
- 65 Lowe RF. The distribution of blood groups and HLA antigens in Zimbabwean Africans. Cent Afric. J. Med. 1988 (Suppl) 27:11-18.
- 66 Binderup L. Lymphocyte-Macrophage co-operation during induction of T-suppressor cell activity in Rats with adjuvant arthritis. Ann. Rheum. Dis. 1983; 42: 687-692.
- 67 Krakauer RS: Disorders of the suppressor cell system in Autoimmunity. PP. 233-236: In Waldmann TA (Moderator); Disorders of suppressor Immunoregulatory cells in the pathogenesis of Immunodeficiency and Autoimmunity. Ann Intern Med. 1978; 88:226-238.
- 68 Latchman DS. Heat shock Proteins in human disease. J. Royal Col. of Physicians of Lon. 1991; 25(4): 295-299.
- 69 Young RA, Elliott TJ. Stress proteins, Infection and Immune Surveillance. Cell 1989; 59:5-8.
- 70 Young RA. Stress Proteins and Immunology. Ann. Rev.

- Immunol 1990; 8: 401-20.
- 71 Winfield JB. Stress Proteins, Arthritis and Autoimmunity
Arthritis Rheum. 1989;32:1497 - 1504.
- 72 La Thangue NB, Latchman DS. A Cellular protein related
to heat shock protein 90 accumulates during herpes
simplex virus infection and is over-expressed in
transformed cells. Exp. Cell Res. 1988; 178:169-79.

APPENDIX I:

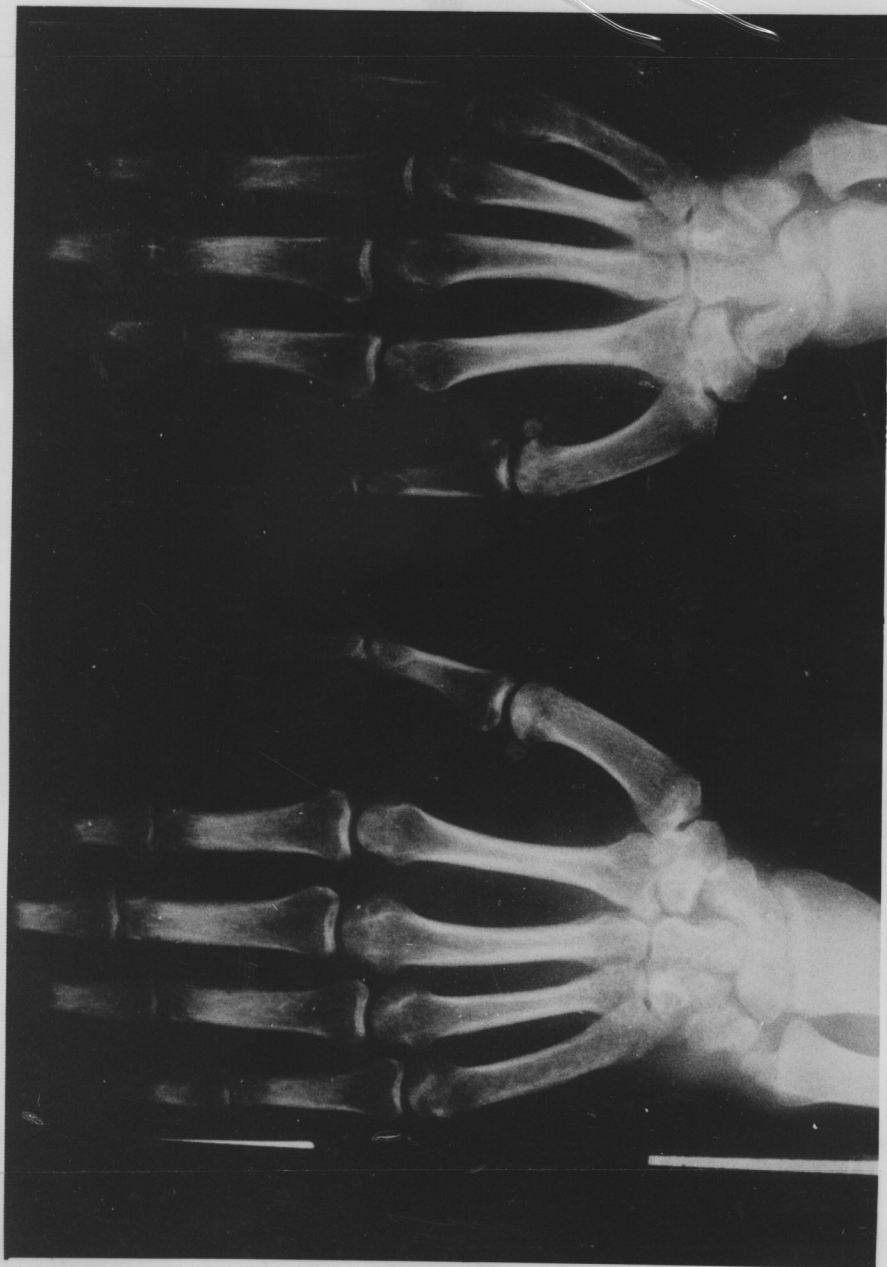


PLATE 1: The hands of a 43 year old man with Reiter's Disease of 8 months duration showing PARIATICULAR OSTEOPOROSIS. Periostitis is also evident in the Right 5th metacarpal.

APPENDIX II



PLATE 2: Right hand Film of a 41 year old men with Reiter's disease of 1 year's duration. It shows periarticular osteoporosis, narrowing of several joint spaces and erosion and sub-luxation of the thumb MCP and IP Joints.

APPENDIX III:



PLATE 3: The left hand Film of a 30 year old man with Reiter's disease. He had had persistent disease for 3 years. Periarticular osteoporosis is evident as well as erosions, ankylosis and sclerosis of the wrist joint, subluxation of the thumb MCP, narrowing of joint spaces and periostitis in the index metacarpal shaft and, as evidenced by expansion of the ends of the proximal and middle phalanges around the PIP joints.

APPENDIX IV



PLATE 4: The left hand film of a 29 year old female with relapsing undifferentiated spondylarthropathy of nearly 5 years duration. It shows Para-articular erosions at the thumb MCP, Middle finger PIP and DIP Joints. Ankylosis at the PIP Joints of the 3rd and 5th fingers as well as Boutonniere deformities of these fingers are evident.



PLATE 5: The hands of a 36 year old woman with persistent undifferentiated spondylarthropathy of 5 year duration. Periarthritic osteoporosis and osteosclerosis are both present as well as pencil-in-cup erosion at the right index MCP, erosions at Right PIP and DIP joints, the left thumb MCP and IP joints, the left 4th finger MCP and PIP joints. There is also loss of joint space at all hand joints. Bony ankylosis of the right 4th and 5th PIP joints and ankylosis of the right

APPENDIX VII



PLATE 7: The right foot of a 41 year old man with undifferentiated spondylarthropathy of 7 months duration. There is extensive erosion of the calcaneal attachments of the achilles tendon and plantar fascia.