East African Medical Journal Vol. 87 No. 10 October 2010
PREVALENCE AND CHARACTERISTICS OF ARTICULAR MANIFESTATIONS IN HUMAN IMMUNODEFICIENCY VIRUS INFECTION
P. E. Ekwom, MBChB, MMed (Internal Medicine) (UoN), Medical specialist II, Department of Medicine, Kenyatta National Hospital. P. O Box 20723 - 00202, Nairobi, G. O. Oyoo, MBChB, MMed (Internal Medicine) (UoN), FACR, Senior lecturer, E. O. Amayo, MBChB, MMed (Internal Medicine) (UoN), FAAN., Associate professor and Chairman, Department of Clinical Medicine and Therapeutics, I. M. Muriithi, MBChB, MMed (Radiol) (UoN), Department of Diagnostic Imaging and Radiation Medicine, Tutorial Fellow, College of Health Sciences, University of Nairobi. P. O. Box 30197, Nairobi, Kenya

Request for reprints: Dr. P. E. Ekwom, Department of Medicine, Kenyatta National Hospital, P. O. Box 20723 - 00202, Nairobi, Kenya

PREVALENCE AND CHARACTERISTICS OF ARTICULAR MANIFESTATIONS IN HUMAN IMMUNODEFICIENCY VIRUS INFECTION

P. E. EKWOM, G. O. OYOO, E. O. AMAYO and I. M. MURIITHI

ABSTRACT

***Background*: Articular manifestations have been reported in HIV infection with a prevalence ranging from 2.5 to 68%.**
***Objectives*: To determine the prevalence, types and characteristics of articular manifestations in the anti-retroviral treatment naive HIV infected patients.**
***Design*: Cross sectional descriptive study.**
***Setting:* Comprehensive care clinic (HIV outpatient clinic) at the Kenyatta National Hospital (KNH) from October 2007 to March 2008.**
***Subjects:* One hundread and ninety three patients; 135 females and 58 males, aged between 19 to 65 years with Human immunodeficiency virus (HIV) infection who were naive to anti - retroviral drug therapy.**
***Main outcome measure*: Presence of articular manifestations that included HIV associated arthritis, HIV associated spondyloarthropathies, HIV associated arthralgia, painful articular syndrome and avascular necrosis.**
***Results:* Thirty three of these 193 patients had articular manifestation with a prevalence of 17.1 %. The type prevalence was; HIV associated arthralgia, 15.6%; undifferentiated spondyloarthropathy, 1 % and HIV associated arthritis; 0.5%. Their mean age was 36 ± 9 years, range 23-63 years; majority were female, male to female ratio of 1: 2.3 and the majority were in World health organization (WHO) clinical staging of HIV infection, class II and III with a mean CD4 cell count of 330 cells/mm^3. Seventeen (51.5%) of the patients with articular disease had oligo - articular presentation, 10(30.3%) mono - articular while 6(18.2%) had poly - articular presentation. The mean duration of joint pains was 53.3 days (range of 2-365 days). Six (18.2%) of these 33 patients missed work, home making activities or school due to the articular disease.**
***Conclusion:* Articular manifestations are common in HIV infection with a prevalence of 17.1 %. HIV associated arthralgia was the most common manifestation. Majority of these patients were female, male to female ratio of 1: 2.3. The mean age of these patients was 36 years with a mean CD4 cell count of 330 cells/mm^3 with 18.2 % of them missing school or work.**

INTRODUCTION

Earliest reports of rheumatologic manifestations in HIV were published in the 1980s. These reports were on the co-occurrence of Reiter's Syndrome and acquired immunodeficiency disease syndrome (1). The prevalence of rheumatic manifestations ranges from 11 to 71.3% (3-5). In these studies, the prevalence of articular manifestations ranges from 2.5- 68%.

HIV associated rheumatic disorders have been recognised all over the world. Seronegative spondyloarthropathies were the most commonly seen articular disorders with a prevalence of 1.7 to 11.2% for reactive arthritis, 1.1 to 5.7% for psoriatic arthritis and between 2.7% and 11.1 % for undifferentiated spondyloathropathy (6).

In Africa there have been numerous reports of HIV associated spondyloathropathy. Davis and Stein (7) described 20 patients in Zimbabwe with reactive

arthritis, incomplete and complete Reiters syndrome. They also reported that there was no association between the development of HIV associated arthropathy and the presence of HLA-8 / 27.

In Zambia, there have been reports of reactive arthritis, psoriatic arthritis and undifferentiated spondyloathropathy associated with HIV (8,9) where overall HIV seroprevalence in the patients with spondyloathropathy was 84% and the prevalence of spondyloathropathy of 180 per 100,000 persons in the HIV infected and 15 per 100,000 in those with no HIV infection (8).

In Congo Brazzaville, prevalence of rheumatologic disease in HIV was 7.2%, 78% of whom had HIV associated arthritis (10).

The reported articular disorders in HIV infection include arthralgia, reactive arthritis, psoriatic arthritis, undifferentiated spondyloathropathy, painful articular syndrome, HIV associated arthritis, septic arthritis, gout and avascular necrosis (11).

MATERIALS AND METHODS

A descriptive cross sectional study of adult patients at the Kenyatta National Hospital's comprehensive care clinic (CCC), a HIV outpatient clinic, who were naive to anti - retroviral therapy, was done between October 2007 and March 2008. The Inclusion criteria were patients aged 13 years and above who were not on anti - retroviral treatment (ART) and gave informed consent.

The exclusion criteria were patients with musculoskeletal rheumatic disorders including rheumatoid arthritis, systemic lupus erythematosus, gout and osteoarthritis or patients with history of direct trauma to the joints. Files of patients at the CCC meeting inclusion criteria were screened and patients were identified.

Patients whose files were selected were informed of the study and consent was obtained. Those who consented were requested to sign the consent forms. A maximum sample of eight patients was obtained per day. Demographic data were collected which included; name, age, gender, occupation and marital status.

The WHO clinical stage of HIV infection (2) was assessed and documented. The patients were screened for articular diseases by the gait, arm, legs and spine (GALS) locomotor screen (12). In patients with positive / abnormal GALS screen, complete medical history and physical examination with emphasis on the musculoskeletal system was carried out as recommended by the American College of Rheumatology ad hoc committee on clinical guidelines (13).

All patients had their CD 4 cell counts determined by flow cytometry, and total blood count and erythrocyte sedimentation rate tests carried out by the standard methods. In those patients with arthritis, rheumatoid factor, antinuclear antibody test, and plasma urate levels were tested. Those patients with hip and alternating buttock pains had plain radiographs of the hip and sacroilliac joints respectively, which were analysed for features of avascular necrosis and sacroilltis by the study's radiologist.

Patients with articular disorders were interviewed as regards severity of pain recorded in a four point Likert scale, effects on activities of daily living, effect on social activities and days missed from work and their global function status by the ACR 1991 revised criteria for global function status in Rheumatoid arthritis (14).

Case definition: An articular manifestation was defined as the presence of one of the following:-
Spondyloarthropathies that is. psoriatic arthritis, reactive arthritis and undifferentiated spondyloathropathy were diagnosed as per the ESSG criteria (25).

Avascular necrosis: diagnosis made on plain radiographic evidence of osteonecrosis as reported by the study's radiologist. Features include, increased radiographic intensity in subchondral bone, thin tangential fracture line below articular surface (crescent sign), distortion of articular surface with sclerosis or discrete fragment seen. The joint retains its normal width.

Infectious arthritis: effusive arthritis with positive synovial fluid culture for causative organism.

Painful articular syndrome: severe intermittent pain in joint(s) and lasting 2-24 hours and requiring hospitalisation or use of narcotic analgesics (11).

HIV associated arthritis: presence of arthritis not meeting ESSG criteria for SpA with negative rheumatoid factor and antinuclear antibody (11).

Arthralgia: pain in the joint(s) without any evidence of synovitis.

STATISTICAL METHODS

Data were collected by use of data collection forms and entered into computer software, statistical package for social sciences (SPSS) version 15.The data were cleaned by running frequencies .By use of the data collection forms all errors of data entry were corrected.

Descriptive statistics for analysis included mean and median for CD4 cell count and age. Proportions and frequency distribution were obtained for all categorical variables which included articular manifestations, gender and functional class.

The mean CD4 cell count was calculated for the various articular manifestations and was compared amongst patients with the articular manifestations and those without using the independent t- test.
The global functional status of the patients with articular manifestations class was summarised in proportions/percentages

The chi square test was used to determine associations between CD4 cell count and articular manifestations. Significance level was set at a 0.05.

ETHICAL CONSIDERATIONS

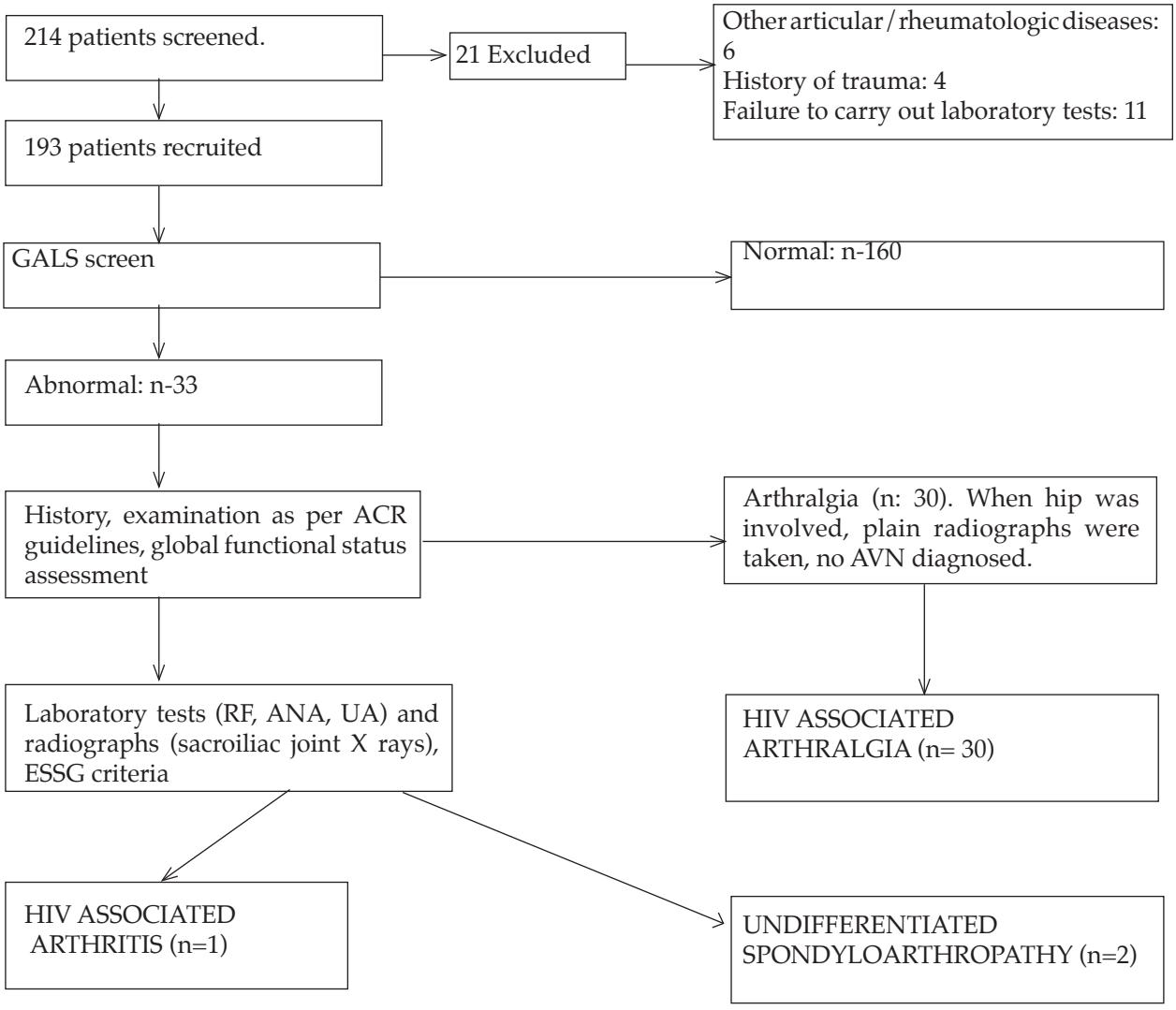
Permission to carry out the study was sought from the department of Medicine, University of Nairobi and the Kenyatta National Hospital, Ethics, Research and Standards committee before commencement of the study. All patients gave informed consent for inclusion into the study and for the relevant tests to be carried.

RESULTS

Between October 2007 and March 2008, 214 patients were seen at the Comprehensive care clinic. twenty one were excluded and 193 enrolled as shown in the following flow chart.

Figure 1

Flow chart of study methods



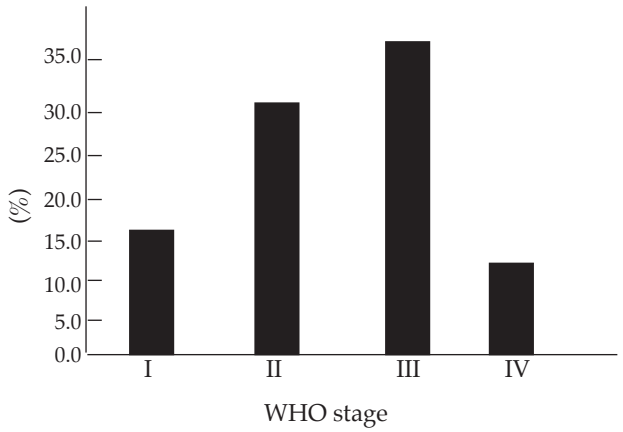
Thirty three of the study patients were diagnosed to have articular disease with a prevalence of articular

manifestations in HIV infection of 17.1% with a 95% CI: 12.1- 22.1%.

The prevalence of various articular manifestations was; HIV associated arthritis, 0.5%, undifferentiated spondyloarthropathy, 1 % and HIV associated arthralgia 15.6%

The mean age for patients with articular disease was 36.03 ± 9.07 years, (range 23-63 years) ten (30.3%) were male with 23 (69.7%) were female giving a male to female ratio of 1:2.3. Majority of the study patients with articular manifestations were in HIV WHO stage II and stage III as shown in figure 2.

Figure 2
HIV associated arthralgia



Thirty (15.6%) of the study patients were diagnosed with HIV associated arthralgia. Their mean age was 37.0 ± 8.8 years, (range 23-65 years) 20 (66.7%) were female and ten (33.3%) were male with male to female ratio of 1: 2. Majority of these patients, 16 (53.3%) had an oligo - articular pattern of joint involvement, 10 (33.3%) mono - articular, while four (13.4%) had poly - articular.

The most commonly involved joint was the knee joint in 17 (53.3%). Other involved joints include; ankle in six (20%), shoulder in four (13.3%), hip in four (13.3%), hand joints in four (13.3%), wrist one (3.3%), joints of the feet in one (3.3%)and elbow in one (3.3%). Four patients with HIV associated arthralgia had hip joint pain. Plain radiographs of the hip did not reveal avascular necrosis.

Majority of these patients with HIV were in WHO stage II and III infection. WHO stage I; six (20%), stage II; nine (30%), stage 111; ten (33.3%) and stage IV; five(16.7%). By the use of a four point Likert type pain scale, nineteen (63.3%) of the patients with HIV associated arthralgia reported mild joint pains, ten (33.3%) had moderate and one (3.3%) severe joint pains. Mean reported duration of joint pain(s) was 51 days with a range of 1-365 days. Five (16.7) % of the patients with HIV associated arthralgia had missed 400 hours of work due to the joint disease. Majority of these patients had no impairment of their function due to the joint disease. seventeen (56.7%) had a global functional status of class I, 9(30%) class II, four (13.3%) class III.

The mean CD4 cell count in these patients was 325.3.The mean CD4 cell count in patients with no articular disease was 362.4 cells/mm3. There was no statistical difference between CD4 cell count in patients with no articular disease and patients with HIV arthralgia with a p - value of 0.837, showing no association between CD4 cell count and HIV associated arthralgia.

HIV associated undifferentiated spondyloarthropathy (uSpA): Two (1%) of the study patients were diagnosed to have undifferentiated spondyloarthropathy. They were both female,23 and 31 years of age. Both presented with arthritis, oligo and poly - arthritis. One had axial involvement. The patient with oligo - arthritis had knee and ankle joint involvement and had a history of alternating buttock pain and had a grade 3 unilateral sacroillitis on plain radiograph.

The patient with poly - arthritis had asymmetric joint involvement with involvement of the wrist joints, knee, ankle, right proximal interphalangeal joint middle finger and left ring finger proximal interphalangeal joint and enthesopathy with sausaging of the fingers.

They both met the ESSG diagnostic criteria for undifferentiated spondyloarthropathy. By use of the four point Likert pain scale, one of the patients reported moderate joint pain whereas the other reported severe pain intensity. The duration of joint pains was 14 and 90 days with a total number of hours missed from work, school or home making of sixty hours. One of these patients had a global functional class II whereas the other had a global functional class IV. Both patients had elevated ESR; ESR of 75 mm/h and106 mm/hr.

Rheumatoid factor and antinuclear antibody tests were negative in these patients and their uric acid levels were within normal range. One patient had a CD4 cell count of 95 cells/mm^3 and the other a CD4 cell count of 327 cells/mm^3. The numbers of patients with undifferentiated spondyloarthropathy were too few to associate occurrence of this disease with CD4 cell count.

HIV associated arthritis: Only one of the study patients was diagnosed to have HIV associated arthritis. She was a 24 year old female tailor who was widowed. She had a polyarthritis with involvement of the hand joints, wrist, shoulder, elbow, knee and joints of the feet. She had asymmetric joint involvement of both the upper and lower limbs.

By use of a four point Likert pain scale, she reported moderate joint pain intensity; she had missed 240 hours of work due to the joint disease

and a global functional status was class IV. Her ESR was 61 mm/hr, rheumatoid factor and antinuclear antibody tests were negative. Uric acid level was within normal range.

Her CD4 cell count was 722 cells/mm3: Statistical tests to find association between CD4 cell count and HIV associated arthritis could not be carried out as there was only one patient with this clinical entity.

Other articular diseases in HIV infection in patients not on anti - retroviral treatment: None of the study patients had septic (infectious) arthritis, reactive arthritis, psoriatic arthritis, painful articular syndrome or avascular necrosis.

DISCUSSION

The threat of the global impact of HIV will change from opportunistic infections to more chronic conditions and musculoskeletal rheumatic conditions is one of these conditions. Musculoskeletal diseases are known to be a major cause of disability in patients.

This study was the first in Kenya and the East African region to document the prevalence, types and characteristics of articular manifestations in HIV infection.

The mean age of 36 years in our patients with articular disease is in keeping with the usual pattern of patients with HIV disease in Kenya and is similar to the mean ages of 28.5 to 34.2 years in patients with rheumatic/articular diseases as reported in other prevalence studies. (3 - 5).

Overall, there were more female than male as compares with data from the National AIDS Control Council (NACC) and National AIDS/STDS control programe (NASCOP) where the prevalence of HIV infection in 2006 in females was 6.7% and in males was 3.5% (15).

The male to female ratio in our study was 1: 2.3 which is unlike studies carried out in the West where the male to female ratio was 4:1 (4), 25:1 (16), and 10:1 (3). In these studies, the mode of HIV transmission was predominantly homosexual unlike in Kenya where it is by heterosexual.

The prevalence of articular diseases in HIV infection has varied according to the study design. In our study, starting from an outpatient HIV population, the prevalence was 17.1% which was within the reported prevalence of 2.5- 68 % (3-5). Munoz *et al* (4) in a retrospective study of 556 patients in Spain, found a prevalence of 2.5%, Calabrese *et al* (16), in a longitudinal prospective study of 117 patients followed for a mean of 24.6 months (range: 0.5-85 months) in the United states of America (USA), found a prevalence of 14.5% whereas Berman *et al* (3) in a prospective study of 101 predominantly male homosexual HIV infected patients in USA, found a prevalence of 68%.

The types of articular manifestations found in our study were three, HIV associated arthralgia with a prevalence of 15.6 %, undifferentiated spondyloarthropathy with a prevalence of 1 % and HIV associated arthritis with a prevalence of 0.5%. HIV associated arthralgia is reported as the most common articular manifestation in HIV infection (3,6,11) which is similar to our finding. The most common pattern of joint involvement is oligoarticular with knee, shoulder and elbow joints involvement. This is similar to our findings.

Undifferentiated spondyloarthropathy is an uncommon disease. The prevalence of undifferentiated spondyloarthropathy was 1 % in our study which is similar to findings in other studies where a prevalence of 0.2% (4) and 2.7% (21) was found.

It is difficult to compare our prevalence with that of other African studies due to differences in study design. In a cohort study of patients with arthritis in the rheumatology clinic in Zambia, Njobvu *et al* (9) found a prevalence of 98% of HIV infection in patients diagnosed with un differentiated spondyloarthropathy.

The pattern of joint involvement in the two patients with undifferentiated spondyloarthropathy was oligo and poly - arthritis and none of the patients had mucocutaneous features. This is similar to the pattern of disease reported in other studies (4, 12, 21).

The prevalence of HIV associated arthritis in this study was 0.5 % which is within the reported prevalence in other studies of 0.4% (4) to 10.8% (18). The pattern was polyarticular which is similar to the reported patterns (19).

None of the patients had septic arthritis. In other studies the prevalence of septic arthritis has ranged from 0-3% (4, 5, and 20) and the common risk factor for the septic arthritis was intravenous drug use. Only one out of our 193 study patients was an intravenous drug user which may explain the absence of this diagnosis during the study period.

Surprisingly, none of the study patients was diagnosed to have reactive arthritis. This is reported as the most common arthritis in HIV infection with a prevalence ranging from 1.7 - 11.1 % (21). This might be explained by the low prevalence of gonorrhea and Chlamydia in Kenya with a prevalence of 1.8- 4.5% (22, 23) and also the absence of documented *Salmonella, Shigella* epidemic during the course of the study.

The absence of reactive arthritis may also be explained by the use of co-trimoxazole prophylaxis which is effective against the organisms that are associated with ente - roreactive reactive arthritis.

In the study in Zambia by Njobvu *et al* (8), the high prevalence of the ente - roreactive reactive

arthritis was attributed to an epidemic of *Shigella dysenteriae*.

None of our study patients was diagnosed with avascular necrosis which has been reported in case reports to occur even in patients not on anti - retroviral treatment (ART) but commonly occur as a complication of ART. Four of our study patients had hip joint pains and plain radiographs of the hip which did not show evidence of avascular necrosis. Plain radiographs are not a sensitive tool to pick out avascular necrosis, and may be some cases of avascular necrosis were missed.

None of our study patients was diagnosed with painful articular syndrome. Only one of the patients presented with a one day ankle joint pain of two hours duration which was of mild intensity and he did not require analgesics and did not fit the study criteria for painful articular syndrome. In other studies, Berman *et al* found a prevalence of 10% (3). The high prevalence in his study might be explained by the fact that majority of his study patients had severe immunosuppression (CDC stage C HIV infection) and the association in literature of the painful articular syndrome with severe immunosuppression (24). Other studies only reported cases of the painful articular syndrome (16, 24).

In this study, no patient was diagnosed with psoriatic arthritis (PsA). In other studies, the prevalence of PsA has ranged from 1-20 % (5). Psoriatic arthritis is reported to be rare in Africans.

We did not find a correlation between articular disease and CD4 cell count which is similar to findings by Casado *et al* (21) who found a poor correlation between musculoskeletal conditions and CD4 cell count. This study shows that 48.5% of patients with articular disease had class III-IV global functional status showing functional impairment with total hours missed from school, work or homemaking activities being 700 hours suggesting that the articular manifestations are not benign and are a cause of disability. Other studies done did not assess the patient's global functional status and therefore we cannot compare with them.

In conclusion, articular manifestation is common in HIV infection with a prevalence of 17.1 %. HIV associated arthralgia was the most common manifestation. Majority of these patients were female. The mean age of these patients was 36 years and majority were females. Their mean CD4 cell count was 330 cells/mm^3 with 18.2 % of them missing school or work.

REFERENCES

1. Winchester, R., Bernstein, D.H., Fischer, H.D., *et al*. The co- occurrence of Reiter's Syndrome and Acquired Immunodeficiency. *Ann of Int. Med*. 1987; **106:**19-26.
2. World health organization (WHO). WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. 2007.
3. Berman, A., Espinoza, L.R., Diaz, J.D., *et al*. Rheumatic Manifestations of human immunodeficiency virus infection. *Am J Med* 1988; **85:** 59 - 64.
4. Munoz, F.S., Cardenal, A., Balsa, A.,*et al*. Rheumatic manifestations in 556 patients with Human Immunodeficiency Virus Infection. *Semin Arthritis Rheum* 1991; **21 :** 30 - 39.
5. Serhal, D. and Calabrese, L.H. Diagnosing and managing rheumatic disorders in HIV infected persons. *J Musculoskel Med*. 2000; **17:**606 - 620
6. Marquez, J., Candia, I., Restrepo, C.S.,*et al*. HIV-associated musculoskeletal involvement. *AIDS reader* 2004**; 14:** 175 - 184.
7. Davis, P. and Stein, M., Human Immunodeficiency Virus -Related Connective Tissue Diseases: A Zimbabwean Perspective. *Rheum Dis Clin North Am* .1991; **17**: 89 - 97.
8. Njobvu, P., McGill, P., Kerr, H.,*et al*. Spondyloathropathy and human immunodeficiency virus infection in Zambia. *J Rheum*.1998; **25**: 1553 - 1559.
9. Njobvu, P. and Mc Gill, P. Psoriatic arthritis and Human Immunodeficiency Virus infection in Zambia. *J Rheum*. 2000; **27**: 1699 - 1702.
10. Ntsiba, H., Njandeu–Singwe, M., Mbou-Essie, D.,*et al*.Musculoskeletal manifestation of HIV in Brazzaville, Congo (abstract). *Clin Rheumatol*.2007; **26**: 31.
11. Mody, G. M., Parke, F. A. and Reveille J. D. Articular manifestations of Human Immunodeficiency Virus Infection. *Best pract res clin rheumatol*. 2003; **17**: 265 - 287.
12. Doherty, M., Dacre, J., Dieppe, P., Snaith, M. The 'GALS' Locomotor Screen. *Ann Rheum Dis*. 1992; **51** : 1165 - 1169.
13. American College of Rheumatology ad hoc committee on clinical guidelines. Guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms. *Arthritis Rheum*.1996; **39**: 1 - 8.
14. Hochberg, M. C., Chang, R. W., Dwosh, I.,*et al*. The American College of Rheumatologists 1991 revised criteria for the classification of global function status in Rheumatoid arthritis. *Arthritis Rheum*. 1992; **35**: 498- 502.
15. The national AIDS control council and the national AIDS/STD control program. National HIV Prevalence in Kenya. June 2007.
16. Calabrese, L. H., Kelley, D. M., Myers, A.,*et al*. Rheumatic symptoms and Human Immunodeficiency Virus infection. The Influence of clinical and laboratory variables in a longitudinal cohort study. *Arthritis Rheum*. 1991; **34**: 257 - 263.
17. Casado, E., Olive, A., Holgado, S.,*et al*. Musculoskeletal manifestations in patients positive for Human Immunodeficiency Virus: Correlation with CD4 count. *J Rheum*. 2001; **28**: 802 - 804.
18. Medina-Rodriguez, F., Guzman, C., Jara, L. J.,*et al*. Rheumatic manifestations in HIV positive and negative individuals: a study of 2 populations with similar risk factors. *J Rheum*. 1993; **20**; 1880 - 1884.

19. Berman, A., Cahn, P., Perez, H.,*et al*. Human Immunodeficiency Virus infection associated arthritis: clinical characteristics. *J Rheum*. 1999; **26**: 1158 - 1162.
20. Vassilopoulos, D., Chalasani, P., Jurado, R.L., *et al*. Musculoskeletal infections in patients with Human Immunodeficiency Virus infection.*Medicine*.1997;**76**: 284 - 294.
21. Cuellar, M. L. and Espinoza, L. R. Rheumatic manifestations in HIV-AIDS. *Best pract res clin rheumatol*. 2000; **14**: 579 - 593.
22. Hawken, M.P., Melis, R.D.J. and Ngombo, D.T. Part time sex workers in a suburban community in Kenya, a vulnerable hidden population. Sex. *Trans infect*. 2002; **78**: 271 - 273.
23. Buve, A.,Weiss, H. and A. Laga, M. The epidemiology of gonorrhoea, chlamydial infection and syphilis in four African cities. The Multicentre study of factors determining the different prevalence of HIV in sub-Saharan Africa .*AIDS*. 2001; **15**: Suppl 4:S79 - S88.
24. Pouchot, J., Simonpoli, A. M., Bortolotti, V.,*et al*. Painful articular syndrome and Human Immunodeficiency Virus Infection. *Arch Int Med*. 1992; **152**: 646 - 649.
25. Dougados, M., van der Linden, S., Juhlin, R.,*et al*. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; **34**: 1218 - 1227.