[Click here to view linked References](#)

1

Title page**Rheumatic diseases in HIV-infected patients in the post-antiretroviral therapy era: a tertiary care center experience**

Konstantinos Parperis, Yasir Abdulqader, Robert Myers, Bikash Bhattarai and Muhsen Al-Ani.

Maricopa Integrated Health System and University of Arizona College of Medicine, Phoenix Campus

Authors:

Konstantinos Parperis, MD, FACP, FACR, Maricopa Medical Center and University of Arizona College of Medicine, 2525 E Roosevelt Street, Phoenix, Arizona, USA, 85008

Yasir Abdulqader, MD, Maricopa Medical Center and University of Arizona College of Medicine, 2525 E Roosevelt Street, Phoenix, Arizona, USA, 85008

Robert Myers, MD, Maricopa Medical Center and University of Arizona College of Medicine, 2525 E Roosevelt Street, Phoenix, Arizona, USA, 85008

Bikash Bhattarai, BVSc, MVSc, PhD, Maricopa Medical Center and University of Arizona College of Medicine, 2525 E Roosevelt Street, Phoenix, Arizona, USA, 85008

Muhsen Al-Ani, MD, University of Washington, 4245 Roosevelt Way NE, Seattle, Washington, USA, 98105

Corresponding author:

Konstantinos Parperis, MD

Address: Maricopa Medical Center and University of Arizona College of Medicine, 2525 E Roosevelt Street, Phoenix, Arizona, USA, 85008

Email: kparperi@email.arizona.edu

Tel: +1-602-344-1095

Abstract

Objective: The aim of the study was to calculate the proportion of rheumatic diseases in HIV patients who were receiving ART and to identify association of the HIV medications with the development of rheumatologic diseases.

Methods: We conducted a retrospective chart review during the period of 2010 to 2016. We identified 2,996 patients as having chronic HIV infection and on ART, and we collected data regarding patient's demographic characteristics, co-morbidities, CD 4 count, HIV viral load and ART.

Results: 113 out of 2996 HIV patients (3.8%) were found to have a rheumatic condition (mean age of 48.6 years, 83% male). The most frequent musculoskeletal condition was avascular necrosis (AVN) in 39 (1.3%) and the most frequent autoimmune condition was psoriasis in 28 patients (1%). Compared with the 200 HIV patients without any diagnosis of rheumatic disease, the patients with rheumatic conditions were older (Mean age of 48.9 vs. 42.7 years; $p<0.01$) and had a longer duration of HIV infection (Mean duration of 15.5 vs. 10.3 years; $p<0.01$). The odds of rheumatic conditions were 1.7 times higher in males (relative to females). Those who received integrase inhibitors were more likely (63.3%) to develop rheumatologic manifestations relative to those who never received integrase inhibitors (21.6%; $p<0.01$).

Conclusion: The proportion of rheumatic diseases in HIV patients appears to be comparable to the prevalence in the US population. Older age, longer duration of HIV infection and the use of ART regimens containing integrase inhibitors, appear to increase the risk of developing a rheumatic condition.

Keywords: HIV, antiretroviral therapy, rheumatic diseases, avascular necrosis, psoriasis

Introduction

Human immunodeficiency virus (HIV) is a cytopathic retrovirus and the cause of AIDS, a chronic viral infection that is characterized by depletion of the CD4+ T-cell count and an immunosuppressive state of the host. Over 36.7 million persons worldwide and 1.2 million in the US have been infected with HIV [1]. A previous lethal disease and a source of substantial morbidity and mortality, it is now considered a chronic condition due to the widespread use of highly effective antiretroviral regimen [2]. Antiretroviral therapy (ART) has increased the life expectancy of patients with HIV infection, however the long-term use of antiretroviral treatment has been associated with a state of chronic inflammation, premature aging and increased risk of cardiovascular disease [3-5].

HIV infection has been associated with a wide variety of rheumatic conditions including HIV-associated arthritis, reactive arthritis, psoriasis and psoriatic arthritis [6,7]. The rheumatic diseases (RD) can occur early in the disease course or later in life.⁸ So far there are few studies in the US, describing rheumatic diseases in the post-ART era [9, 10].

The primary aim of this study was to determine the prevalence and the different types of RD associated with well-controlled HIV, as well as the patient characteristics and potential risk factors associated with the development of RD.

Material and Methods

In the present study, 2,996 patients with HIV infection on ART were identified during the period of January 2010 to April 2016 by using the international classification of diseases (ICD) 9 and 10 codes database at the Maricopa Medical Center in Phoenix, Arizona. ICD-9 and ICD-10 codes used to identify patients with RD included rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease associated spondyloarthropathy, reactive arthritis, systemic lupus erythematosus, sjogren's syndrome, dermatomyositis, polymyositis, systemic sclerosis, granulomatosis with polyangiitis, microscopic polyangiitis, Takayasu's arteritis, giant cell arteritis, gout, calcium pyrophosphate crystal deposition disease, septic arthritis, avascular necrosis, osteoarthritis, fibromyalgia. Among the 2996 patients, we identified 113 patients with a diagnosis of RD based on diagnostic codes and the diagnosis was confirmed by individual medical record review by a rheumatologist based on history, exam, laboratory and imaging findings.

Inclusion criteria were HIV-infected adult patients on ART, seen in the outpatient HIV clinic at least 2 times, have been adherent with their regimen, with well-controlled disease, not hospitalized over the past year for any reason, and diagnosed with RD at least 6 months after the diagnosis of HIV infection.

Exclusion criteria were as follows: patient with a new diagnosis of HIV, uncontrolled disease state with detectable HIV viral loads, seen in the HIV clinic once, hospitalized over the past year, diagnosed with a RD before the HIV infection or during the first 6 months after the HIV infection.

The HIV diagnosis was based on a positive ELISA test, confirmed by the Western blot test.

The group without rheumatic conditions included 200 adult patients with HIV on ART, randomly selected, without any evidence of RD recorded in the last clinic visit. RD was excluded based on history, physical exam and available laboratory tests reported in the chart.

We collected data including age, gender, BMI, ethnicity, history of smoking or alcohol abuse, co-morbidities, age of diagnosis of HIV, age of diagnosis of rheumatic diseases and antiretroviral regimen.

Laboratory data were collected as follows: mean HIV viral load, mean CD 4 T-cell count, antinuclear antibody (ANA), extractable nuclear antibodies (ENA), rheumatoid factor (RF), cyclic citrullinated protein – antibody (CCP), antineutrophil cytoplasmic antibodies (ANCAs), complement 3, complement 4, cryoglobulins, hepatitis B and C antibodies, HLA B27 and uric acid level.

The institutional review board and the ethics committee of the Maricopa Integrated Health System approved the study before the collection of data (approval number 2015-126). Due to retrospective nature of the study no informed consent was obtained.

Statistical Analysis

Descriptive summaries of all the patients and group level measures were reported. Assumptions of normality (Shapiro-Wilk) and homogeneity of variance (Levene's test) were performed. Group differences were statistically compared and presented using Mann-Whitney U and Fisher's exact test, respectively for continuous and categorical variables. Odds ratios and 95% confidence intervals of rheumatic conditions were reported using specific patient characteristics, comorbidities, and drugs as the exposure Statistical Package for Social Sciences (SPSS) version 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and OpenEpi (OpenEpi.com).

Results

Of the 113, patients with RD, 83% were males. The most frequent RD was avascular necrosis (AVN) in 39 patients (1.3%) confirmed by MRI imaging. The most common autoimmune disease was psoriasis in 28 patients (1%). Seven patients had rheumatoid arthritis (0.23%), 6 (0.2%) had psoriatic arthritis and 6 (0.2%) had systemic lupus erythematosus. Ankylosing spondylitis, granulomatosis with polyangiitis and polymyositis were present in one case each. In regard to crystal induced arthritis we identified 10 patients with crystal proven Gout (0.35%) and 1 with Calcium Pyrophosphate Crystal Deposition Disease. Infectious musculoskeletal conditions were present in 14 patients (0.5%), 11 with osteomyelitis and 3 with septic arthritis.

Of the 113 patients with RD, 83% were males. The group of HIV patients without RD consisted of 200 patients with a mean age of 42.7 years (Table 1). Compared with patients without RD, patients with RD were older (mean age of 48.9 vs. 42.7 years; $p < 0.01$) and had a longer duration of HIV infection (mean duration of 15.5 vs. 10.3 years; $p < 0.01$).

The odds of RD were 1.7 times higher in males relative to females ($P=0.132$). Those who received integrase inhibitors were more likely (63.3%) to develop rheumatologic manifestations relative to those who never received integrase inhibitors (21.6%; $p < 0.01$) (Table 2).

HIV patients with co-morbidities including hepatitis C infection, chronic kidney disease chronic obstructive pulmonary disease had higher risk developing a RD ($p < 0.05$) (Table 3). We found similar prevalence of common rheumatic diseases such as psoriasis and psoriatic arthritis in our patient population when compared with the general population (Table 4).

Discussion

Previous reports suggested that patients with untreated HIV infection untreated have a higher risk developing musculoskeletal symptoms and RD [11]. RD that have been described in HIV patients include HIV-associated arthritis, articular painful syndrome, seropositive rheumatoid arthritis, seronegative spondyloarthropathies (including Psoriatic Arthritis, Reactive arthritis), systemic Lupus erythematosus and vasculitis [8]. Since the introduction of combination ART, a significant decline of the occurrence of rheumatic manifestations has been reported, but new conditions have been emerged including the avascular necrosis (AVN) and the immune reconstitution inflammatory syndromes [9]. In this study, we investigated the prevalence of RD in the HIV patient population in a county

hospital and to our knowledge this one of the largest retrospective study number of HIV patients in the US. Among 2996 patients included in our study, we identified 113 patients (3.7%) with a diagnosis of a RD. The most common rheumatic conditions were AVN and psoriasis. We found that longer duration of the disease and older age were associated with higher risk of development of RD in the HIV population; the CD4 count and viral load levels were not associated with higher risk of RD. In addition, those with a comorbid condition like hepatitis C were more likely to have higher risk of developing a RD.

We did not observe a higher risk of RD in our HIV-population, with the exception of ANV, and the results of our study are consistent with previous studies [12-14]. In a US prospective longitudinal cohort study of 395 HIV-infected patients on ARTs, demonstrated a significant decline in the rate of RD including connective tissue diseases, psoriatic arthritis and reactive arthritis [9].

Our study complements results reported by Yang et al. showing that the prevalence of autoimmune arthritis in the HIV-infected Taiwanese population was similar to the general population [14]. The authors retrospectively reviewed the records of 3623 HIV infected patients and they found 10 patients with ankylosing spondylitis, 6 with rheumatoid arthritis, 1 with psoriatic arthritis and 1 with Sjogren's syndrome [14]. A recent Taiwanese cohort study reported a higher standardized incidence higher for psoriasis, autoimmune hemolytic anemia, uveitis in HIV patients on ART compared with the general population, but lower for rheumatoid arthritis and ankylosing spondylitis [15]. This result is in line with the low prevalence of autoimmune diseases reported by Viro et al., a cross-sectional study of 5186 HIV –infected patients from France that found only one case of rheumatoid arthritis and one of systemic lupus erythematosus [16].

AVN was the most frequent RD affecting 39 patients. HIV patients have higher risk of developing AVN, mainly in the hip, consistent with previous reports [17,18]. Although previous case reports implicate protease inhibitors as a possible cause of AVN, larger case control studies didn't support this link [18-20]. The association between HIV infection and development of AVN and can be multifactorial including HIV-infection, ART combination, hyperlipidemia and steroid use [21,22]. Interestingly we found an association between that the use of integrase inhibitors and the development of AVN. Integrase inhibitors are newer antiretroviral agents and it's hard to extrapolate any conclusions because HIV patients have an increase for AVN and further studies are needed in order to validate our findings.

The most prevalent autoimmune rheumatic disease in our study was psoriasis with prevalence of 1% and psoriatic arthritis with 0.2%. The prevalence of psoriatic arthritis in the general population is 0.25%, and psoriasis 1-2%, very similar with our results, which may imply that HIV patients on antiretroviral treatment don't seem to have an increased risk of developing the above diseases [23, 24]. Consistent with previous findings, the prevalence of rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis and crystal induced arthropathies was similar or even less prevalent compared with general population due to male predominant HIV population [25]. No cases of reactive arthritis were identified and that can be explained by the fact that reiter's syndrome was described mainly in patients with acute HIV infection and most cases prescribed were before the era of ART [6]. We identified that co-morbidities like hepatitis C infection, chronic kidney disease, diabetes are potential risks factors for the development of rheumatic disease. Tsui et al. observed that patients with HIV and hepatitis C infection were more likely to experienced musculoskeletal pain compared with patients without hepatitis C but a more recent study didn't confirm this finding[26, 27].

The prevalence of musculoskeletal infections including septic arthritis and osteomyelitis was 0.5%, consistent with previous reports [28]. Vassilopoulos et al. conducted a retrospective study of estimated 3000-4000 patients with HIV and found an estimated incidence of 0.75% of musculoskeletal infections and the common risk factor was history of IV drug use [28].

Our study has potential limitations. First, we retrospectively collected the data and we found a relatively small sample of patients with rheumatic and musculoskeletal diseases. Another limitation is that our study population is mainly from one healthcare system and our findings may be generalizable only to similar healthcare system

In conclusion our findings indicate that the proportion of RD appears comparable or even less common to the prevalence of the general population with the exception of AVN. Possible explanation is that HIV infected population predominately by men, who have a reduced lifetime risk of developing a rheumatic disease when compared with the female patients. The most prevalent rheumatic condition in HIV patients on ART was AVN and autoimmune rheumatic disease was psoriasis.

Acknowledgements: The authors thank Napatkamon Ayutyanont for support with statistical analysis.

Conflicts of Interest: We have no conflict of interest to declare. We full control of all primary data and we agree to allow the journal to review our data if requested.

Ethical standards: The institutional review board and the ethics committee of the Maricopa Integrated Health System approved the study before the collection of data (approval number 2015-126). Due to retrospective nature of the study no informed consent was obtained.

References

1. UNAIDS. Global AIDS update, 2016. [Internet. Accessed August 1, 2017.] Available from: www.unaids.org/sites/default/files/media_asset/global-AIDS-update-2016_en.pdf
2. Pahan MA, Van Natta ML, Palella FJ, Addessi A, Meinert C, Lewis RA, et al (2010) Excess mortality in patients with AIDS in the era of highly active antiretroviral therapy: temporal changes and risk factors. *Clin Infect Dis* 51:947–956
3. Aberg JA (2012) Aging, inflammation, and HIV infection. *Top Antivir Med* 20:101–105
4. Brothers TD, Rockwood K (2014) Biologic aging, frailty, and age-related disease in chronic HIV infection. *Curr Opin HIV AIDS* 9:412–414
5. Freiberg MS, Chang CC, Kuller LH, et al (2013) HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med* 173:614–622
6. Winchester R, Bernstein DH, Fischer HD, Enlow R, Solomon G (1987) The co-occurrence of Reiter's syndrome and acquired immunodeficiency. *Ann Intern Med* 106:19-26
7. Reveille JD, Conant MA, Duvic M (1990) Human immunodeficiency virus-associated psoriasis, psoriatic arthritis, and Reiter's syndrome: a disease continuum? *Arthritis Rheum* 33:1574-1578
8. Kaye BR (1989) Rheumatologic manifestations of infection with human immunodeficiency virus (HIV). *Ann Intern Med* 111:158-167
9. Calabrese LH, Kirchner E, Shrestha R (2005) Rheumatic complications of human immunodeficiency virus infection in the era of highly effective antiretroviral therapy emergence of a new syndrome of immune reconstitution and changing patterns of disease. *Semin Arthritis Rheum* 35:166-174
10. Maganti RM, Reveille JD, Williams FM (2008) Therapy insight: the changing spectrum of rheumatic disease in HIV infection. *Nat Clin Pract Rheumatol* 4:428-438
11. Medina-Rodriguez F, Guzman C, Jara LJ, et al (1993) Rheumatic manifestations in human immunodeficiency virus positive and negative individuals: a study of 2 populations with similar risk factors. *J Rheumatol* 20: 1880-1888

12. Helmick CG, Felson DT, Lawrence RC, et al (2008) Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I Arthritis Rheum 58:15-25
13. Lawrence RC, Felson DT, Helmick CG, et al (2008) Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 58:26-35
14. Yang JJ, Tsai MS, Sun HY, et al (2015) Autoimmune diseases-related arthritis in HIV-infected patients in the era of highly active antiretroviral therapy. J Microbiol Immunol Infect 48:130-136
15. Yen YF, Chuang PH, Jen IA, et al (2016) Incidence of autoimmune diseases in a nationwide HIV/AIDS patient cohort in Taiwan, 2000-2012. Ann Rheum Dis 76:661-665
16. Viro E, Duclos A, Adelaide L, et al (2017) Autoimmune diseases and HIV infection: A cross-sectional study. Medicine (Baltimore) 96:e5769
17. Miller KD, Masur H, Jones EC, et al (2002) High prevalence of osteonecrosis of the femoral head in HIV-infected adults. Ann Intern Med 137:1-25
18. Martin K, Lawson-Ayayi S, Miremont-Salamé G, et al (2004) Symptomatic bone disorders in HIV-infected patients: incidence in the Aquitaine cohort (1999-2002). HIV Med. 5:421-426.
19. Meyer D, Behrens G, Schmidt RE, Stoll M (1999) Osteonecrosis of the femoral head in patients receiving HIV protease inhibitors. AIDS 13:1147-48
20. Bongiovanni M, Chiesa E, Riva A, d'Arminio Monforte A, Bini T (2003) Avascular necrosis of the femoral head in a HIV-1 infected patient receiving lopinavir/ritonavir. Int J Antimicrob Agents 22:630-31
21. Scribner AN, Troia-Cancio PV, Cox BA, et al (2000) Osteonecrosis in HIV: a case-control study. J Acquir Immune Defic Syndr 25:19-25
22. Mary-Krause M, Billaud E, Poizot-Martin I, et al (2006) Risk factors for osteonecrosis in HIV-infected patients: impact of treatment with combination antiretroviral therapy. AIDS 20:1627-1635
23. Fox C, Walker-Bone K (2015) Evolving spectrum of HIV-associated rheumatic syndromes. Best Pract Res Clin Rheumatol 29:244-458
24. Ouédraogo DD, Ntsiba H, Tiendrébéogo Zabsonré J, et al (2014) Clinical spectrum of rheumatologic diseases in a department of rheumatology in Ouagadougou (Burkina Faso). Clin Rheumatol 33:385-89

25. Lau CS, Li P (2017) Epidemiology: The effects of AIDS on the prevalence of rheumatic diseases. *Nat Rev Rheumatol* 13:8-10
26. Tsui JI, Cheng DM, Libman H, Briden C, Samet J (2012) Hepatitis C virus infection is associated with painful symptoms in HIV-infected adults. *AIDS Care* 24:820-27
27. Ogdie A, Pang WG, Forde KA, et al (2015) Prevalence and risk factors for patient-reported joint pain among patients with HIV/hepatitis C coinfection, hepatitis C mono-infection, and HIV mono-infection. *BMC Musculoskelet Disord* 16:93
28. Vassilopoulos D, Chalasani P, Jurado RL, Workowski K, Aquilino CA (1997) Musculoskeletal infections in patients with human immunodeficiency virus infection. *Medicine (Baltimore)* 76:284-294

Table 1: Characteristics of HIV patients with and without rheumatic conditions in the post antiretroviral therapy period in a safety net hospital

Characteristics	Patient groups	Mean	SD	Minimum	Maximum	Median	P*
Age	Non-rheumatic	42.7	11.4	22	69	42	<0.001
	Rheumatic condition	48.9	10.7	22	77	50	
BMI	Non-rheumatic	26.0	5.4	3	41	25	0.642
	Rheumatic condition	25.9	5.9	16	46	26	
Years with HIV	Non-rheumatic	10.3	7.5	1	36	8	<0.001
	Rheumatic condition	15.5	8.1	2	34	16	
Current CD4	Non-rheumatic	594	334	4	2281	572	0.036
	Rheumatic condition	522	347	13	1435	458.5	
Previous CD4	Non-rheumatic	586	314	13	1624	571	0.023
	Rheumatic condition	518	349	6	1754	426	
Current viral load	Non-rheumatic	21391	181193	0	2335721	0	0.638
	Rheumatic condition	9050	37537	0	252316	0	
Previous viral load	Non-rheumatic	20260	161408	0	2085573	0	0.822
	Rheumatic condition	58350	501845	0	5260607	0	

* Wilcoxon rank sum 2 sided P

Table 2: Association of rheumatic and non-rheumatic disease patients with their history of receiving specific antiretroviral drugs

ARTs	Ever received	Rheumatic condition (%)	None (%)	Odds ratio (95% CI)	P*
NRTI	NRTI Never	104 (37.28) 9 (26.47)	175 (62.72) 25 (73.53)	1.0 (0.6 to 1.7)	0.259
NNRTI	NNRTI Never	33 (37.08) 80 (35.71)	56 (62.92) 144 (64.29)	1.1 (0.6 to 1.8)	0.896
Integrase Inhibitor	Integrase inhibitor Never	69 (63.3) 44 (21.57)	40 (36.7) 160 (78.43)	6.3 (3.8 to 10.4)	<0.001
PI	PI Never	31 (26.5) 82 (41.84)	86 (73.5) 114 (58.16)	0.5 (0.3 to 0.8)	0.007
Cobicistat	Cobicistat Never	20 (34.48) 93 (36.47)	38 (65.52) 162 (63.53)	0.9 (0.5 to 1.7)	0.880
Total		113	200		

*Fisher exact two sided P

Table 3: Association of rheumatic and non-rheumatic disease patients with their history of comorbidities

Comorbidities		Rheumatic condition (%)	None (%)	Odds ratio (95% CI)	P*
Hypertension	Hypertension	10 (32.26)	21 (67.74)	0.8 (0.4 to 1.8)	0.698
	No hypertension	103 (36.52)	179 (63.48)		
Hyperlipidemia	HLD	12 (33.33)	24 (66.67)	0.9 (0.4 to 1.8)	0.854
	No	101 (36.46)	176 (63.54)		
Hepatitis B	HepB	2 (66.67)	1 (33.33)	3.6 (0.3 to 40)	0.296
	No	111 (35.81)	199 (64.19)		
Hepatitis C	HepC	10 (90.91)	1 (9.09)	19.3 (2.4 to 153)	<0.001
	No	103 (34.11)	199 (65.89)		
CKD	CKD	7 (87.5)	1 (12.50)	13.1 (1.6 to 108)	0.004
	No	106 (34.75)	199 (65.25)		
Diabetes mellitus	DM	9 (75)	3 (25.00)	5.7 (1.5 to 21.4)	0.010
	No	104 (34.55)	197 (65.45)		
COPD	COPD	6 (100)	0	Not Estimable	0.002
	No	107 (34.85)	200 (65.15)		
Total		113	200		

*Fisher exact two sided P

Table 4: The prevalence of psoriasis and psoriatic arthritis in HIV-infected patients with rheumatic disease and the general population

	Prevalence in HIV infected patients with rheumatic diseases	Prevalence in the general population ^{12,13}
Psoriasis	1%	1-3%
Psoriatic arthritis	0.2%	0.25%