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ORIGINAL ARTICLE

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

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## Abstract

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. We conducted a retrospective chart review during the period of 2010 to 2016. We identified 2996 patients as having chronic HIV infection and on ART, and we collected data regarding patient's demographic characteristics, comorbidities, CD 4 count, HIV viral load, and ART. One hundred thirteen 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 were the older patients with rheumatic conditions (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%; $p < 0.01$). 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** Antiretroviral therapy · Avascular necrosis · HIV · Psoriasis · Rheumatic diseases

## 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 USA have been infected with HIV [1]. A previous lethal disease and a source of substantial morbidity and mortality, 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 (RDs) can occur early in the disease course or later in life [8]. So far, there are few studies in the USA describing RDs 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, 2996 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

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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, Sjögren'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, and 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 two 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, comorbidities, age of diagnosis of HIV, age of diagnosis of RDs, 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 comorbidities including hepatitis C infection, chronic kidney disease, and chronic obstructive pulmonary disease had higher risk developing a RD ($p < 0.05$) (Table 3). We found similar prevalence of common RDs, 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 have a higher risk developing musculoskeletal symptoms and RD [11]. RD that has been described in HIV patients includes HIV-associated arthritis, articular painful syndrome, seropositive rheumatoid arthritis, seronegative spondyloarthropathies (including psoriatic, arthritis, and

**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 | 21,391 | 181,193 | 0 | 2,335,721 | 0 | 0.638 |
| | Rheumatic condition | 9050 | 37,537 | 0 | 252,316 | 0 | |
| Previous viral load | Non-rheumatic | 20,260 | 161,408 | 0 | 2,085,573 | 0 | 0.822 |
| | Rheumatic condition | 58,350 | 501,845 | 0 | 5,260,607 | 0 | |

*Wilcoxon rank sum two-sided *P*

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 is of the largest retrospective study number of HIV patients in the USA. 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]. 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 Sjögren's syndrome [14].

**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 | 104 (37.28) | 175 (62.72) | 1.0 (0.6 to 1.7) | 0.259 |
| | Never | 9 (26.47) | 25 (73.53) | | |
| NNRTI | NNRTI | 33 (37.08) | 56 (62.92) | 1.1 (0.6 to 1.8) | 0.896 |
| | Never | 80 (35.71) | 144 (64.29) | | |
| Integrase inhibitor | Integrase inhibitor | 69 (63.3) | 40 (36.7) | 6.3 (3.8 to 10.4) | < 0.001 |
| | Never | 44 (21.57) | 160 (78.43) | | |
| PI | Pl | 31 (26.5) | 86 (73.5) | 0.5 (0.3 to 0.8) | 0.007 |
| | Never | 82 (41.84) | 114 (58.16) | | |
| Cobicistat | Cobicistat | 20 (34.48) | 38 (65.52) | 0.9 (0.5 to 1.7) | 0.880 |
| | Never | 93 (36.47) | 162 (63.53) | | |
| 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 | Hep B | 2 (66.67) | 1 (33.33) | 3.6 (0.3 to 40) | 0.296 |
| | No | 111 (35.81) | 199 (64.19) | | |
| Hepatitis C | Hep C | 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*

A recent Taiwanese cohort study reported a higher standardized incidence higher for psoriasis, autoimmune hemolytic anemia, and 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 Virot 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 did not support this link [18–20]. The association between HIV infection and development of AVN 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; it is 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 RD 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 in which psoriasis is 1–2%. Very similar with our results may imply that HIV patients on antiretroviral treatment do not 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 comorbidities like hepatitis C infection, chronic kidney disease, diabetes are potential risks factors for the development of RD. Tsui at el. 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 did not 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].

**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 |

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 RD when compared with the female patients. The most prevalent rheumatic condition in HIV patients on ART was AVN and autoimmune RD was psoriasis.

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## Compliance with ethical standards

**Disclosures** None.

**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.

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