

## To Study Rheumatological Manifestations in HIV-Positive Patients

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### ABSTRACT

**Introduction:** Rheumatological manifestations (RM) are quite common among HIV-Positive patients. The aim of this study was to determine the prevalence of such manifestations and to study their relationship with different biochemical parameters and the Centers for Disease Control and Prevention (CDC) stage of HIV.

**Objectives:** To determine the prevalence of various rheumatological manifestations found in HIV-positive patients and to evaluate different biochemical parameters and their correlation with rheumatological manifestations in HIV positive adult patients.

**Material and Methods:** This was an observational cross-sectional study done on 500 HIV-positive patients aged more than 18 years who attended the OPD/ART Center at GMC/Rajindra Hospital Patiala, a tertiary care hospital. Patients recruited in the study underwent preliminary evaluation by a detailed history including age, sex, and ART status, followed by evaluation of rheumatological manifestations and their correlation to different biochemical parameters such as Hb, ESR, serum uric acid, RA factor, CRP, VDRL, and CD4 cell count.

**Results:** In our study, the mean age of patients was  $38.39 \pm 13.8$  years with 75.40 % of patients in the age group of 18-47 years. 27.80% were females and 72.20% were males. 48.40% of patients were in CDC Stage 2, 30% in CDC Stage 3, and 21.60% in CDC Stage 1. The mean CD4 cell count was  $375.32 \pm 410.55$  cells/microliter. 55% of the patients had rheumatological manifestations. Various types of RM found were arthralgias (28.4%), myalgias (23.2%), arthritis (12.6%), uveitis (5.2%), psoriasis (3.8%), tendo Achilles enthesitis (3.4%), keratoderma blenorrhagicum (2.4%), plantar fasciitis (2.4%), vasculitis (2.2%), and diffuse infiltrative lymphocytosis syndrome (DILS) (0.8%). The most common RM found was arthralgias with knees being the most common joints involved followed by ankles, shoulders, and elbows. Myalgia was the

second most common RM. In arthritis, asymmetric oligoarthritis was the most common type, knees were the most commonly involved joints followed by the ankles, PIP, MCP, hip, elbow, DIP, shoulder, wrist, and MTP. HIV-Associated arthritis was the most common type found in 9% of patients, while Rheumatoid Arthritis, Psoriatic Arthritis, and Reactive Arthritis were seen in 4 cases each (0.8% of patients). Septic Arthritis and Undifferentiated spondyloarthropathy accounted for 0.6% of patients each (3 cases). RM were associated with older age ( $p=0.001$ ), female gender ( $p=0.001$ ), advanced CDC stage ( $p=0.001$ ), patient on ART ( $p=0.001$ ), raised ESR ( $p=0.001$ ), positive CRP ( $p=0.001$ ), and hyperuricemia ( $p=0.004$ ). No correlation of anemia ( $p=0.103$ ), RF ( $p=0.100$ ), VDRL ( $p=0.999$ ), and ANA ( $p=0.149$ ) was found with RM.

**Conclusion:** In our study, 55% of patients had rheumatic manifestations. Older patients, females, and patients with advanced CDC stages have higher chances of RM. These rheumatological manifestations result in increased morbidity in HIV-positive patients. Thus, early identification of these problems is necessary to manage these patients and reduce morbidity associated with these conditions.

**Keywords:** RM, CDC Stage, HIV Associated Arthritis.


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### INTRODUCTION

Human immunodeficiency virus (HIV) is an RNA virus that causes acquired immunodeficiency syndrome (AIDS). It is a slowly progressive immune deficiency that is usually characterized by

the initial phase of clinical latency. If left untreated it gradually progresses to cause one or more serious events, known as AIDS-defining illnesses. AIDS is a collection of opportunistic infections

commonly experienced by HIV immunocompromised patients. HIV is a serious global public health concern. Around 39 million people were living with HIV infection at the end of 2022.<sup>[1]</sup> India is the third-largest HIV center in the world. In India, the prevalence of HIV is about 0.21%, and about 2.4 million people are living with HIV.<sup>[2]</sup>

People living with HIV are highly prone to various neurological, inflammatory, and rheumatological diseases and opportunistic infections.<sup>[3]</sup> Rheumatological manifestations (RM) in HIV patients can occur at any stage of the disease, but these are more often seen in the late stages. Winchester et al. described the RM in HIV patients for the first time.<sup>[4]</sup>

The presence of these in the settings of severe immunodeficiency and immunosuppression is itself paradoxical. Rheumatological manifestations may occur because of the infection by HIV itself, B cell activation, and subsequent circulating immune complexes. A switch from Th1 to Th2, autoantibodies, hypergammaglobulinemia, and subsequent increased expression and release of cytokines are other possible mechanisms. HIV infections also share many similarities with a wide variety of autoimmune diseases, including a substantial polyclonal B cell activation that is associated with a high incidence of antiphospholipid antibodies such as anticardiolipin antibodies, VDRL antibodies, and lupus-like antibodies. Also, there is an increased incidence of antinuclear antibodies.<sup>[5,6]</sup>

Various rheumatological manifestations that can be found in HIV patients are arthralgias, myalgias, HIV-associated arthritis, reactive arthritis, septic arthritis, undifferentiated spondyloarthritis (SpA), osteomyelitis, diffuse infiltrative lymphocytosis syndrome (DILS), painful articular syndrome, vasculitis, etc.<sup>[7]</sup>

This study was undertaken to assess the spectrum and the pattern of rheumatological involvement in HIV patients and their relationship with different factors.

## MATERIALS AND METHODS

This cross-sectional study was conducted at the Department of Medicine, Government Medical College & Rajindra Hospital, Patiala, among 500 HIV-Positive patients to evaluate the spectrum of various RM. The patients were recruited over 1 year attending the OPD/ART Center at Rajindra Hospital Patiala.

Patients diagnosed with Hepatitis B, C, Hepatitis B and C co-infection, immunodeficiency states (other than HIV), or patients who were already diagnosed case of a rheumatological disease before the patient was diagnosed as HIV positive were excluded from the study.

Patients recruited in the study had a preliminary evaluation by a detailed history including age, sex, duration of ART, CDC stage, any associated co-morbidity, past treatment records, and detailed physical examination. Patients were classified into their respective CDC Stages based on their CD4+ T-lymphocyte cell count into 1-3 stages. Patients were also classified based on their age, gender, and whether the patient was on ART or not (newly diagnosed). Relevant investigations such as Hb, ESR, serum uric acid, RA factor, CRP, VDRL, and ANA were done and data collected was recorded.

### Statistical Analysis

The collected data was analyzed using SPSS statistics software 21.0 Version. To describe the data descriptive statistics, frequency analysis, and percentage analysis were used for categorical

variables and the mean & SD were used for continuous variables. To find the significance in categorical data, the Chi-Square/ Fisher Exact test was used. The p-value of < 0.05 was considered statistically significant.

## RESULTS

In our study, the mean age of patients was  $38.39 \pm 13.8$  years. The majority of patients (75.40%) were in the age group 18-47 years. 27.80% were females and 72.20% were males. 48.40% of patients were in CDC Stage 2, 30% in CDC Stage 3, and 21.60% in CDC Stage 1. The mean CD4 cell count was  $375.32 \pm 410.55$  cells/microliter. The demographic data and correlation of RM are given in Table 1. RM were more common in older age groups (p-value= 0.001), female sex (p-value= 0.001), patients with advanced CDC stage (p-value= 0.001), and patients on ART (p=0.001). Patients with raised ESR (p=0.001), with positive CRP (p=0.001), and with hyperuricemia (p=0.004) were associated with RM. No correlation of anemia (p-value= 0.103), RF (p-value=0.100), ANA (p-value=0.053), and VDRL (p=0.999) was found with RM.

Various types of RM found were arthralgias (28.4%), myalgias (23.2%), arthritis (12.6%), uveitis (5.2%), psoriasis (3.8%), tendo Achilles enthesitis (3.4%), keratoderma blenorrhagicum (2.4%), plantar fasciitis (2.4%), vasculitis (2.2%), and DILS (0.8%). The most common RM found was arthralgias with knees being the most common joints involved followed by ankles, shoulders, and elbows. Myalgia was the second most common RM. In arthritis, asymmetrical oligoarthritis was the most common type, knees were the most commonly involved joints followed by the ankles, PIP, MCP, hip, elbow, DIP, shoulder, wrist, and MTP. HIV-Associated arthritis was the most common type found in 9% of patients, while Rheumatoid Arthritis, Psoriatic Arthritis, and Reactive Arthritis were seen in 4 cases each (0.8% of patients). Septic Arthritis and Undifferentiated spondyloarthropathy accounted for 0.6% of patients each (3 cases).

In our study, we also found that older HIV patients had significantly higher chances of having anemia (p=0.001) and positive CRP (p=0.007). However, no correlation of age was found with ESR (p=0.189), uric acid (p=0.487), VDRL (p=0.899), RF (p=0.431), and ANA (p=0.099) in HIV-positive patients. HIV-positive females had moderately higher chances of having positive CRP (p=0.043). However, no correlation of gender was found with anemia (p=0.200), ESR (p=0.172), RF (p=0.371), VDRL (p=0.214), hyperuricemia (p=0.650), ANA (p=0.869) in HIV-positive patients. Patients with higher CDC Stage had significantly higher chances of having anemia (p=0.001), raised ESR (p=0.001), positive CRP (p=0.007), and hyperuricemia (p=0.004). However, no correlation of the CDC Stage was found with VDRL (p=0.611), RF (p=0.569), and ANA (p=0.212). ART was found to be associated with anemia (p=0.21) and raised ESR (p=0.001). No significant correlation of ART was found with CRP (p=0.885), RF (p=0.106), VDRL (p=0.956), hyperuricemia (p=0.805), and ANA (p=0.948).

## DISCUSSION

RM in HIV-positive patients was first described by Winchester et al.<sup>[4]</sup> In our study, the prevalence of RM was 55%. Xuan Zhang et al<sup>[8]</sup>, A Berman et al<sup>[9]</sup>, and Renu Saigal et al<sup>[10]</sup> documented a prevalence of 54.08%, 71.3%, and 46.67% respectively. Kaddu-Mukasa M et al<sup>[11]</sup> and Praveen Kumar Yadav and B Jayakumar<sup>[12]</sup>

**Table 1: RM and various biochemical parameters in HIV-Positive patients**

	RM present	RM absent	
<b>Age group-</b>			Fisher's Exact= 19.382
<b>Mean age</b>	40.54±14.30	35.76±12.86	
18-32 Years	99(45%)	121(55%)	p-value= 0.001
33-47 Years	97(61.78%)	60(38.22%)	
48-62 Years	50(58.82%)	35(41.18%)	
≥63 Years	29(76.32%)	9(23.68%)	
<b>Gender</b>			X <sup>2</sup> = 15.387
Female	96(69.06%)	43(30.94%)	p-value= 0.001
Male	179(49.58%)	182(50.42%)	
<b>Mean CD4 count</b>	316.87 ± 227.08	446.75 ± 550.54	X <sup>2</sup> = 25.629
<b>CDC stage</b>			p-value= 0.001
1	45(41.67%)	63(58.33%)	
2	123(50.83%)	119(49.17%)	
3	107(71.33%)	43(28.67%)	
<b>ART</b>			X <sup>2</sup> = 14.298
On ART	143(64.41%)	79(35.59%)	p-value= 0.001
Not on ART (newly diagnosed)	132(47.48%)	146(52.52%)	
<b>Anemia</b>			X <sup>2</sup> = 2.654
<b>Mean Hb ± SD</b>	12.55±1.45 125(59.24%)	12.88±1.30 86(40.76%)	p-value= 0.103
Present	150(51.90%)	139(48.10%)	
Absent			
<b>ESR</b>			X <sup>2</sup> = 14.125
<b>Mean ± SD</b>	38.62±13.35 243(58.84%)	23.17±5.17	p-value= 0.001
Raised	32(36.78%)	170(41.16%)	
Not raised		55(63.22%)	
<b>CRP</b>			X <sup>2</sup> = 10.759
Positive	21(87.50%)	3(12.50%)	p-value= 0.001
Negative	254(53.36%)	222(46.64%)	
<b>RF</b>			X <sup>2</sup> = 2.706
Positive	6(85.71%)	1(14.29%)	p-value=0.100
Negative	269(54.56%)	224(45.44%)	
<b>VDRL</b>			X <sup>2</sup> = 0.001
Positive	11(55%)	9(45%)	p-value=0.999
Negative	264(55%)	216(45%)	
<b>S. Uric Acid</b>			X <sup>2</sup> = 8.453
<b>Mean ± SD</b>	7.31±0.18	5.04±0.76	p-value=0.004
Hyperuricemia	41(73.21%)	15(26.79%)	
Normal	234(52.70%)	210(47.30%)	
<b>ANA</b>			X <sup>2</sup> = 3.73
Positive	11(n=79, 13.92%)	3(n=67, 4.48%)	p-value=0.053
Negative	68(n=79, 86.08%)	64(n=67, 95.52%)	

**Table 2: Various types of RM and their prevalence**

RM	N	Percentage among Total patients (n=500)	Percentage among Patients with RM (n=275)
Arthralgia	142	28.40%	51.63%
Myalgia	116	23.20%	42.18%
HIV Associated Arthritis	45	9%	16.36%
Uveitis	26	5.20%	9.45%
Psoriasis	19	3.80%	6.91%
Tendo-Achilles enthesitis	17	3.40%	6.18%
Keratoderma Blenorrhagicum	12	2.40%	4.36%
Plantar Fasciitis	12	2.40%	4.36%
Vasculitis	11	2.20%	4%
Reactive Arthritis	4	0.80%	1.45%
Rheumatoid Arthritis	4	0.80%	1.45%
Psoriatic Arthritis	4	0.80%	1.45%
DILS	4	0.80%	1.45%
Septic Arthritis	3	0.60%	1.09%
Undifferentiated SpA	3	0.60%	1.09%

found the prevalence of RM to be 27% and 25.2%. The higher prevalence in our study may be because 78.4% of patients were in CDC Stages 2 and 3.

Our study signified the presence of RM in older age groups ( $p=0.001$ ). This can be attributed to the fact that with the advent of ART, the life expectancy of patients has increased thus increasing the various rheumatological manifestations in older patients. RM are in general found more in females. Our study also showed female preponderance ( $p\text{-value}=0.001$ ). This study also signified that low CD4 cell counts are more associated with the presence of RM. This was also seen in Renu Saigal et al.<sup>[10]</sup> Our study also showed a correlation between ART and RM ( $p=0.001$ ), 64.41% of patients on ART had RM while 48% of patients not on ART (newly diagnosed) had RM. This was in contrast to Renu Saigal et al.<sup>[10]</sup> where the opposite was found to be significant. Chiowchanwisawakit P et al.<sup>[13]</sup> showed no correlation between the use of ART and RM.

In our study, we found a positive correlation between ESR and RM ( $p\text{-value}=0.001$ ). Renu Saigal et al.<sup>[10]</sup> also reached the same conclusion. Santa Naorem et al.<sup>[14]</sup> also found a positive correlation between ESR and HIV-associated arthritis and fibromyalgia. We also found a correlation between CRP and RM ( $p\text{-value}=0.001$ ). Santa Naorem et al.<sup>[14]</sup> also established a correlation between CRP and HIV-associated arthritis ( $p=0.001$ ) and fibromyalgia ( $p=0.04$ ). Rheumatoid Factor was found positive in 1.4% ( $n=7$ ) of patients. Of these 7 patients, 6 patients had RM. VDRL was found positive in 4% ( $n=20$ ) of patients ( $p=0.999$ ). In the study conducted by Renu Saigal et al.<sup>[10]</sup>, VDRL was found positive in 5.33% of patients. In our study hyperuricemia was found in 11.2%. A significant correlation was seen between hyperuricemia and RM ( $p=0.004$ ). Hyperuricemia was seen in 10.67% of patients in the study conducted by Renu Saigal et al.<sup>[10]</sup> ANA was randomly done on 146 patients. There was no significant correlation found between ANA positivity and RM ( $p=0.149$ ).

The most common RM seen was arthralgias, found in 142 cases. The most commonly involved joints were the knees ( $n=65$ ) followed by the ankles ( $n=25$ ), shoulders ( $n=24$ ), and elbows ( $n=14$ ). The remaining 9.86% of patients with arthralgias had PIP, DIP, MCP, and wrist joint involvement. In the study conducted by Renu Saigal et al.<sup>[10]</sup>, the prevalence of arthralgias was documented to be 26.67%. In a study by Praveen Kumar Yadav and B Jayakumar<sup>[12]</sup>, arthralgias were seen in 8.83% of patients. In a study by Santa Naorem et al.<sup>[14]</sup>, arthralgias were seen in 22.51% of patients. In a study conducted by Alakes et al.<sup>[15]</sup>, arthralgias were found in 26.7% of patients. In all these studies, the knees were the most commonly involved joint.

After arthralgias, myalgias were the next most common RM in HIV-positive patients. 23.2% of patients in our study had myalgias. While, in the study conducted by Alakes et al.<sup>[15]</sup>, 46.67% of patients had myalgias. Praveen Kumar Yadav and B Jayakumar<sup>[12]</sup> found the prevalence of myalgias to be 4.67%. In the study by Renu Saigal et al.<sup>[10]</sup>, the prevalence of myalgias was 18.67%. A Azami et al.<sup>[16]</sup> found myalgias to be seen in 3.5% of patients.

In our study, arthritis was seen in 12.60% of patients with oligoarthritis being the most common (57.14%), followed by monoarthritis (30.16%) and polyarthritis (12.70%). Of these patients, 57.14% had asymmetrical involvement. The most commonly involved joints were the knees followed by the ankles, PIP, MCP, hip, elbow, DIP, shoulder, and wrist. In a study

conducted by Renu Saigal et al.<sup>[10]</sup>, arthritis was seen in 13.33% of cases. The knees were the most commonly involved joint followed by ankles and PIP joints. O Rogeaux et al.<sup>[17]</sup> found arthritis in 6.6% of cases.

In our study, rheumatoid arthritis was diagnosed in 4 cases (0.8% of total patients). In a study conducted by Renu Saigal et al.<sup>[10]</sup>, rheumatoid arthritis was seen in 1.33% of cases, while RF was positive in 2 cases (2.67%). Alakes et al.<sup>[15]</sup> conducted a study and found the prevalence of rheumatoid arthritis to be 0.7% (seen in 2 cases). In a study conducted by Q Yao et al.<sup>[18]</sup>, Rheumatoid arthritis was seen in 1 case (0.1%).

Psoriasis was seen in 19 cases (3.8% of total patients) and 4 cases (0.8% of total patients) had psoriatic arthritis. All cases had asymmetrical involvement with two cases having oligoarthritis and two having polyarthritis. Two cases had associated uveitis while one had associated Tendo- Achilles enthesitis. In a study conducted by Q Yao et al.<sup>[18]</sup> and A Azami et al.<sup>[16]</sup> psoriatic arthritis was not seen. In a study conducted by Renu Saigal et al.<sup>[10]</sup>, psoriatic arthritis was seen in 1.33% of cases, while psoriasis was found in 2.67%. In a study done by Javier Marquez et al.<sup>[19]</sup>, psoriatic arthritis was seen in 2.66%.

Reactive arthritis was seen in 4 cases (0.8% of total patients). Three of the cases were preceded by diarrhea while 4th case had undocumented infection. The involvement was asymmetrical in all cases with the knee joint being the most commonly involved. All four cases had associated keratoderma blenorrhagicum while three cases had uveitis. In a study conducted by Renu Saigal et al.<sup>[10]</sup>, reactive arthritis was seen in 2.67% of cases. D Buskila et al.<sup>[20]</sup> found reactive arthritis in 4% of cases. In a study conducted by Fernandez S et al.<sup>[21]</sup>, reactive arthritis was found in 0.5%.

Undifferentiated SpA was seen in 3 cases (0.6% of total patients). Xuan Zhang et al.<sup>[8]</sup> found no case of spondyloarthritis. In studies conducted by Renu Saigal et al.<sup>[10]</sup> and K Narayanan et al.<sup>[22]</sup>, undifferentiated SpA was seen in 4% and 0.4% of cases. Praveen Kumar Yadav and B Jayakumar<sup>[12]</sup> found undifferentiated SpA in 11.3% of cases.

Features of septic arthritis were seen in 3 patients (0.6% of total patients). The culture showed growth of staphylococcus aureus in two cases while in the third case, no growth was found. In studies conducted by Renu Saigal et al.<sup>[10]</sup>, Javier Marquez et al.<sup>[19]</sup>, and Praveen Kumar Yadav and B Jayakumar<sup>[12]</sup>, septic arthritis was found in 1 cases (1.33%), 6 cases (8%) and 9 cases (1%) respectively.

HIV Associated Arthritis was seen in 45 cases (9% of total patients). Oligoarthritis being the most common one, was found in 64.44% followed by monoarthritis (31.11%) and polyarthritis (4.45%). The involvement was symmetrical in 51.11% and asymmetrical in 48.89%. The knee joints were most commonly involved followed by ankles, DIP, shoulder, PIP, MCP, hip, and elbows. In studies conducted by Kaddu-Mukasa M et al.<sup>[11]</sup> and Renu Saigal et al.<sup>[10]</sup>, HIV-associated arthritis was seen in 4.3% and 2.67% of cases. However, Alakes et al.<sup>[15]</sup> found no case of HIV-associated Arthritis.

DILS was seen in 4 cases (0.8% of total patients). These patients had painless parotid swelling and complaints of dry eyes and mouth. In a study conducted by Williams FM et al.<sup>[23]</sup>, 3% of cases had DILS. Xuan Zhang et al.<sup>[8]</sup> found DILS in 11.22%. In studies conducted by Chen M et al.<sup>[24]</sup> and Renu Saigal et al.<sup>[10]</sup>, the prevalence of DILS was found to be 0.28% and 1.33%. However,

Q Yao et al<sup>[18]</sup> and Alakes et al<sup>[15]</sup> found no case of DILS in their study.

Vasculitis was seen in 11 cases. In a study conducted by Xuan Zhang et al<sup>[9]</sup>, the prevalence of vasculitis was found to be 20.41%. However, K Narayanan et al<sup>[22]</sup> and Alakes et al<sup>[15]</sup> found no case of vasculitis in their study. Renu Saigal et al<sup>[10]</sup> found the prevalence of vasculitis to be 1.33%.

Uveitis was seen in 26 cases. This was associated with other diseases such as psoriatic arthritis in 2 cases, reactive arthritis in 3 cases, and undifferentiated spondyloarthritis in 2 cases. Keratoderma Blenorrhagicum was seen in 12 cases. 4 of the cases were associated with reactive arthritis. In a study conducted by Renu Saigal et al<sup>[10]</sup>, Keratoderma Blenorrhagicum was seen in 1.33% of cases. Tendo-Achilles enthesitis was found in 17 cases. Planter fasciitis was seen in 2.4% of cases. Whereas Renu Saigal et al<sup>[10]</sup>, documented the prevalence of both these conditions at 2.67%. Javier Marquez et al<sup>[19]</sup> found the prevalence of enthesitis to be 2.6%.

## CONCLUSION

The present study suggests that RM can be found in more than half of the patients (55% of the patients). The most common of these RM were arthralgia, myalgia, and arthritis. Older patients, female sex, patients with advanced CDC stages, and patients on ART have higher chances of having RM. Though the exact pathogenesis of RM in HIV-Positive patients is unknown, early identification of these problems is necessary to manage these patients and reduce morbidity associated with these conditions.

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