Original Article

Prevalence of Rheumatological Manifestations in HIV Infected Patients in a Tertiary Care Centre In Eastern India : A Prospective Observational Study

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Background : Highly active, viral suppressive Anti-retroviral Therapy (ART) has significantly increased the life expectancy of HIV infected patients, which increases precipitation of age related diseases and comorbidities. Nowadays, Rheumatological Manifestations are being recognized as an important contributor of morbidity in PLHIV.

Aims : The aim of our study was to determine the prevalence of Rheumatological Manifestations in ART naive PLHIV and during the first six months of ART initiation.

Settings and Design : The prospective observational study was conducted in the School of Tropical Medicine, Kolkata.

Materials and Methods : Newly diagnosed ART naive HIV infected patients were recruited. Clinically and Serologically for Rheumatologic Manifestations and followed up period for next six months.

Statistical analysis used : Statistical analysis was performed R version 4.0.2 and $p \leq 0.05$ was considered significant.

Results : We recruited 106 ART naive patients and followed them up for six months after initiation of ART. Forty-three ART naïve patients (40.6%) had Rheumatological Manifestations. The most common Rheumatological condition was HIV arthralgia (28.3%) followed by rheumatoid Arthritis (3.8%), Systemic Lupus Erythematosus (SLE) (2.8%), Osteoarthritis (0.9%), Myositis (1.9%), Psoriatic Arthritis (0.9%) and Reactive Arthritis (0.9%). Large Joint pain (Knee, Ankle, Hip in decreasing order) was the most common (38.7%) presenting symptom. Musculoskeletal adverse drug reaction of ART occurred in 6.6% patients over the period of six months. HIV clinical stage and CD4 count had no predictive role for the Rheumatological Manifestations. All participants were asymptomatic at the end of six months follow-up.

Conclusions : Timely assessment and management of Rheumatologic Manifestations along with ART initiation may result in favourable outcome in PLHIV.

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***Key words* : HIV, PLHIV, ART naive, Rheumatological manifestations.**

As of 2020, approximately 37.7 million people are living with HIV (PLHIV) all over the world[1]. Availability of effective combination Anti-retroviral Therapy (ART) has increased life expectancy in People Living with HIV (PLHIV)[2,3]. The availability of ART has led to the changing spectrum of Rheumatological conditions[4]. ART regimens may themselves have Rheumatological adverse effects[5], which need to be carefully distinguished. The World Health Organization now recommends initiation of ART in PLHIV as early as possible regardless of CD4 count[6]. HIV arthralgia, Fibromyalgia, Rheumatoid Arthritis, Avascular Necrosis, Systemic Lupus Erythematosus, Polymyositis, Vasculitis, Osteomyelitis are some common Rheumatological Manifestations in HIV seropositive individual. Increasing life expectancy of PLHIV precipitating Rheumatological Manifestations along with aging which is responsible for significant morbidity needed further attention than ever.

Editor's Comment :

- Rheumatological manifestations are important contributors of morbidity in HIV infected patients.
- The most common manifestation in Anti-retroviral Therapy naïve patients is HIV arthralgia.
- Early diagnosis and treatment Rheumatological conditions along with Anti-retroviral Therapy has positive impact on quality of life by reducing Rheumatological morbidity in HIV infected patients.

Materials and Methods

This prospective observational study was performed in the ART centre of a Tertiary Care Hospital of Eastern India from July, 2019 to May, 2020. We recruited adult ART naïve patients. Clinical assessment was performed

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before the initiation of ART and all participants were evaluated for presence of Rheumatological conditions. Specific investigations were performed in cases of suspected Rheumatological Manifestations. Autoimmune profile was also performed when needed which included Rheumatoid Factor (RF), Anti-Cyclic Citrullinated Peptides (anti-CCP) and Anti-nuclear Antibodies (ANA). Diagnosis of HIV arthralgia was done primarily by exclusion.

ART was initiated in all participants and they were subsequently followed up for six months. Monthly assessment was performed in all participants except those who were lost to follow up. All patients with Rheumatological Manifestations received standard treatment for the condition as seen fit by the treating physician. Rheumatologic diseases were diagnosed according to the guidelines of American College of Rheumatology[7-9].

Ethical clearance was obtained from the Clinical and Research Ethics Committee of the institution. Informed consent was obtained from all study participants before recruitment to the study.

The statistical analysis was performed using the R software package version 4.0.2 by the R Foundation for Statistical Computing. The comparison of findings was done by T-test for continuous variables and McNemar's test for categorical variables. Between group analysis was done by Fisher's exact test. Regression models were used to test the predictive value of variables. A $p<0.05$ was taken as significant during the analysis.

Results

A total number of 106 patients were recruited to the study. Four patients were lost to follow up and the rest were followed up for a duration of six months.

Among the 106 participants, 75 (70.8%) had one or more opportunistic infections before initiation of ART. Coinfection with Hepatitis B was found in three patients. Majority of the study participants (69.8%) had WHO clinical stage 3 or 4 disease at baseline[10].

During the final follow-up at the end of six months, several laboratory parameters showed significant improvement ($p<0.05$) including ESR, CRP, Total bilirubin, Conjugated bilirubin, Albumin, SGOT, SGPT, Alkaline Phosphatase and CD4 count (Table 1).

The mean CD4 count at baseline was 211 cells/μL and it was 332 at the end of six months follow-up ($p<0.001$). Immune Reconstitution Inflammatory Syndrome occurred in 5.7% patients (Table 2).

Forty-three patients (40.6%) were found to have Rheumatological Manifestations before initiation of ART.

Table 1 — *Laboratory parameters at baseline and at the end of six months follow-up*

Parameters	Baseline Mean	Follow-up Mean	P-value
Haemoglobin (gm/dl)	11.1	11.4	0.268
WBC (cells/dl)	5.5×10^3	6.2×10^3	0.005
Platelets (cells/dl)	240×10^3	223×10^3	0.099
ESR (mm/1st hour)	137.6	40.5	<0.001
CRP (mg/L)	50.7	5.9	<0.001
Total bilirubin (mg/dl)	0.7	0.5	0.004
Conjugated bilirubin (mg/dl)	0.4	0.2	<0.001
Albumin (gm/dl)	2.7	3.9	<0.001
Globulin (gm/dl)	4.8	4.9	0.943
SGOT (IU/L)	130.7	33.9	<0.001
SGPT (IU/L)	81.4	35.4	<0.001
Alkaline phosphatase (IU/L)	580.2	106.7	<0.001
Urea (mg/dl)	21.7	20.9	0.480
Creatinine (mg/dl)	0.9	0.9	0.892
Uric acid (mg/dl)	4.9	5.0	0.346
CD4 count (cells/μL)	211	332	<0.001

Table 2 — *CD4 count in relation to the Rheumatological Manifestations*

Rheumatological conditions	Mean CD4 count (cells/μL)	Median CD4 count (cells/μL)
HIV arthralgia	199	178
Psoriatic arthritis	307	307
Reactive arthritis	46	46
Myositis	113	113
Osteoarthritis	309	309
Rheumatoid arthritis	284	318
Systemic Lupus Erythematosus	266	366

The most common Rheumatological condition was HIV Arthralgia (28.3%).Other conditions included Rheumatoid Arthritis (3.8%), Systemic Lupus Erythematosus (SLE) (2.8%), Osteoarthritis (0.9%), Myositis (1.9%), Psoriatic Arthritis (0.9%) and Reactive Arthritis (0.9%) (Fig 1).

Large (Knee, Ankle, Hip in decreasing order) Joint pain was the most common presenting symptom (38.7%) among the study participants while other

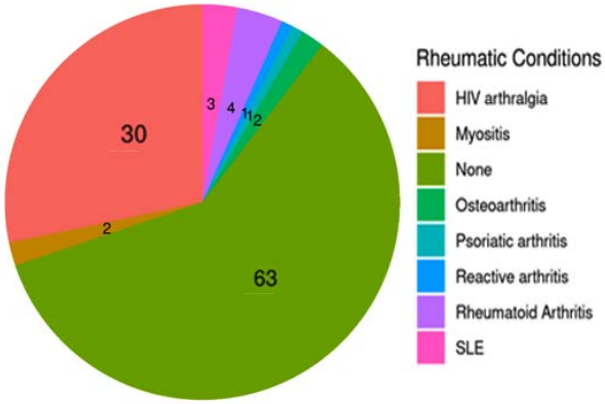

Fig 1 — Proportion of rheumatological conditions at baseline (n=106)

symptoms like skin rash, morning stiffness and muscle weakness was present in 2.8%, 1.9% and 1.9% participants respectively.

ANA was positive in 5.7%, Rheumatoid Factor was positive in 3.8% and anti-CCP was positive in 3.8% study participants.

Regression model was used to determine the predictive value of different parameters on the Rheumatological Manifestations. P<0.05 on multivariate analysis was taken as significant in this case. Presence of joint pain, sites of joint involvement and less than one month of symptoms were found to be predictive of HIV arthralgia on multivariate analysis. Muscle weakness for more than one month was predictive of myositis whereas joint pain for more than one-month, high C-reactive Protein (CRP) and high Platelet Count was predictive of Osteoarthritis. The significant predictors of Rheumatoid Arthritis were joint pain for more than three months along with RF and anti-CCP. Similarly, parameters with predictive value for SLE included skin rash, joint pain for more than one-month, female sex, low haemoglotherapy. However, musculoskeletal adverse drug reaction developed in 6.6% patients over the period of six months. At the end of six months all participants were symptom-free (Fig 2).

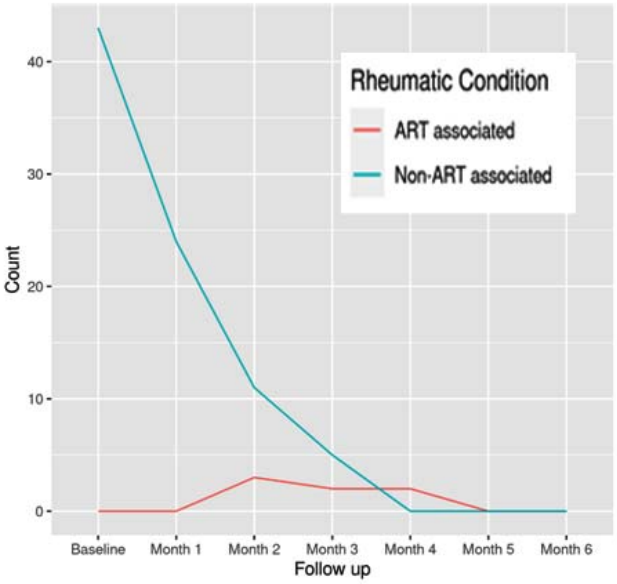

Fig 2 — Trends of rheumatological conditions over the six months follow-up period

Discussion

In our study the prevalence of Rheumatological Manifestation of HIV was found to be 40.6% in ART naïve population. Most common presentation was joint pain 38.7%) and the most common Rheumatological condition was HIV Arthralgia (28.3%).

Although clinical assessment was found to have predictive role in diagnosing Rheumatological conditions, no such association was found with the clinical stage of HIV or the CD4 count of the patients. Presence of opportunistic infections also had no predictive role.

Improvement of laboratory parameters over the period of six months could be attributed to resolution of opportunistic infections, treatment of comorbidities as well as improved clinical status of the patients after initiation of ART.

Although ANA was positive in 5.7% patients at baseline, only 50% of them were diagnosed with SLE and the rest had no Rheumatological condition. However, all the patients with positive RF and anti-CCP were diagnosed with Rheumatoid Arthritis.

The loss to follow-up was only 3.8% and the adherence to the ART regimen was 98%. At the end of six-months follow-up all participants were free of opportunistic infections and the increase of CD4 count was significant (p<0.001). During the follow-up period of six months, only 6.6% patients developed musculoskeletal adverse reactions due to ART, none of them requiring a change of ART regimen.

All participants with Rheumatological Manifestations responded well to therapy and at the end of six months all of them were free of symptoms. Although deformity persisted in patients with Rheumatoid Arthritis.

Another study similar to ours conducted in Eastern India found the prevalence of Rheumatological Manifestation to be 63.3% in ART naïve PLHIV as well as within 6 weeks of ART initiation[11]. Another study conducted in India found the prevalence of Rheumatological Manifestations to be 46.7%[12]. The prevalence of Rheumatological Manifestations vary widely between the studies with some studies showing a prevalence as low as 3.8%[13]. In comparison, the prevalence of rheumatologic conditions was 40.6% in our study.

Our study was limited by the sample size and the short duration of follow-up which was inadequate to detect relatively uncommon Rheumatological Manifestations as well as Rheumatological Manifestations that may happen after six months of ART. We also could not assess cytokines to evaluate its predictive role in Rheumatological Manifestations. A baseline HIV viral load could not be obtained as well.

Although Rheumatological Manifestation is prevalent (40.6%) in ART naïve PLHIV, timely administration of ART as well as adequate

management can resolve the conditions. Although ART regimens themselves may cause musculoskeletal adverse reactions, the prevalence is generally low (<4%).

The HIV clinical stage or the CD4 count had no significant predictive role in Rheumatological Manifestations. Other studies on the Rheumatological Manifestations of HIV also support this finding[14,15]. Although RF and anti-CCP is associated with Rheumatoid Arthritis, specific diagnosis of SLE was reached in only 50% patients with positive ANA.

Our study suggests that all ART naive PLHIV should be assessed for Rheumatological Manifestations and timely management of these conditions in addition to ART may result in a favourable outcome.

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References

1 UNAIDS. Global HIV & AIDS statistics — Fact sheet [Internet]. UNAIDS. 2020 [cited 2021 Jan 10]. Available from: https://www.unaids.org/en/resources/fact-sheet
2 Phanuphak N, Gulick RM — HIV treatment and prevention 2019: current standards of care. *Curr Opin HIV AIDS* 2020; **15(1):** 4-12.
3 Teeraananchai S, Kerr S, Amin J — Life expectancy of HIV-positive people after starting combination antiretroviral therapy: a meta-analysis. *HIV Med* 2017; **18(4):** 256-66.
4 Vega LE, Espinoza LR — Human immunodeficiency virus infection (HIV)-associated rheumatic manifestations in thepre- and post-HAART eras. *Clin Rheumatol* 2020; **39(9):** 2515-22.
5 Reveille JD, Williams FM — Rheumatologic complications of HIV infection. *Best Pract Res Clin Rheumatol* 2006; **20(6):** 1159-79.
6 World Health Organization — Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach [Internet]. Geneva: World Health Organization; 2021 [cited 2021 Oct 1]. (WHO Guidelines Approved by the Guidelines Review Committee). Available from: http://www.ncbi.nlm.nih.gov/books/NBK572729/
7 Hochberg MC, Altman RD, April KT — American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res* 2012; **64(4):** 465-74.
8 Singh JA, Saag KG, Bridges SL — American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis: ACR RA TREATMENT RECOMMENDATIONS. *Arthritis Rheumatol* 2016; **68(1):** 1-26.
9 Singh JA, Guyatt G, Ogdie A — American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis Rheumatol* 2019; **71(1):** 5-32.
10 World Health Organization — Interim WHO clinical staging of HVI/AIDS and HIV/AIDS case definitions for surveillance: African Region. World Health Organization; 2005.
11 Kole A, Roy R, Kole D — Musculoskeletal and rheumatological disorders in HIV infection: Experience in a tertiary referral center. *Indian J Sex Transm Dis AIDS* 2013; **34(2):** 107.
12 Saigal R, Chakraborty A, Yadav RN — Rheumatological Manifestations in HIV-Positive Patients: A Single-Center Study. *Adv Ther* 2020; **37(10):** 4336-45.
13 Parperis K, Abdulqader Y, Myers R — Rheumatic diseases in HIV-infected patients in the post-antiretroviral therapy era: a tertiary care center experience. *Clin Rheumatol* 2019; **38(1):** 71-6.
14 de Filippis LG, Scibilia G, Caliri A — Rheumatic symptoms in patients with human immunodeficiency virus are related to levels of tumor necrosis factor-alpha but not to viral load. *Int J Tissue React* 2005; **27(1):** 9-13.
15 Kulthanan K, Jiamton S, Omcharoen V — Autoimmune and rheumatic manifestations and antinuclear antibody study in HIV-infected Thai patients. *Int J Dermatol* 2002; **41(7):** 417–22.

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