

# Musculoskeletal manifestations in pediatric patients infected with human immunodeficiency virus: Developing country perspective

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## Abstract

**Objective:** Musculoskeletal manifestations in children infected with human immunodeficiency virus (HIV) are responsible for increased morbidity and decreased quality of life. Even in this era of highly active anti-retroviral therapy (HAART), there are limited studies on different rheumatological manifestations in pediatric patients with HIV, and the spectrum of musculoskeletal manifestation in pediatric HIV is yet to be established.

**Methods:** A single-center, prospective, observational study was carried out from October 2014 to September 2016 in a tertiary care hospital of Eastern India with 517 children infected with HIV aged between 3 and 19 years. Particulars of musculoskeletal involvement were at first screened with pediatric gait, arm, leg, spine (pGALS) screening protocol, followed by detailed examination in patients identified through screening. All the participants were re-examined at three and six months of follow-up.

**Results:** Musculoskeletal manifestations were found in 11.2% of the study population. The most common non-infective manifestation found in the study population was arthralgia (5.22%), followed by myalgia (3.29%). The prevalence of definite arthritis was found to be 6/1000 children, whereas infective manifestations (including arthritis, myositis, and osteomyelitis) were found in 2.12% of study population. Musculoskeletal manifestations were commonly found in children infected with HIV who were on anti-retroviral drugs. These manifestations were found commonly in the children in the second decade of their lives. Malnutrition, advanced stage of HIV infection (WHO clinical stage 4), lower CD4 count at the time of evaluation, and longer duration of disease were associated with increased frequency of musculoskeletal manifestations.

**Conclusion:** Musculoskeletal manifestations are frequent in pediatric population infected with HIV. But for better delineation, further multicentric studies are warranted in future in children infected with HIV.

**Keywords:** Children, HIV, musculoskeletal, pGALS



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## Introduction

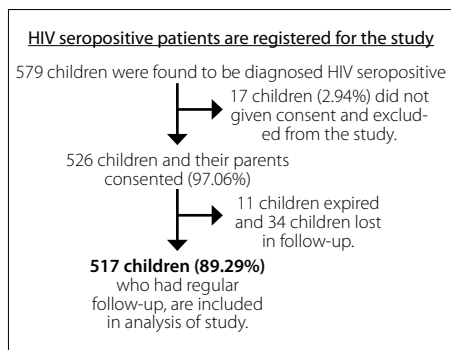
Human immunodeficiency virus (HIV) infection is prevalent worldwide, with India harboring the third largest number of people with HIV/acquired immunodeficiency syndrome (AIDS) infection, 3% of whom are children (1). Worldwide, the total number of children infected with HIV has been estimated at 3.2 million, majority of whom are living in sub-Saharan Africa (2). Children living with HIV/AIDS (CLHIV) form a vulnerable subsection, and may frequently present with clinical symptoms in the first year of life itself. Irrespective of CD4 status, any child aged below 5 years infected with HIV should be started on highly active anti-retroviral therapy (HAART) at the earliest to avoid severe damage to his/her immature immune system.

Musculoskeletal manifestations comprise an immensely important but often neglected group of co-morbidities among CLHIV. The early symptoms of musculoskeletal manifestations as well as the progression of the ailments are often neglected by the patients not only due to the simultaneous presence of the primary disease and/or other life-threatening co-morbidities but also due to their overall lower quality of life. Majority of the studies on rheumatological manifestations in patients with HIV have been done in adults (3-9). A few studies have reported rheumatological problems in pediatric patients with HIV, mostly from North America and Africa (10-15), but to the best of our knowledge, no large-scale prospective study is available from the Asian

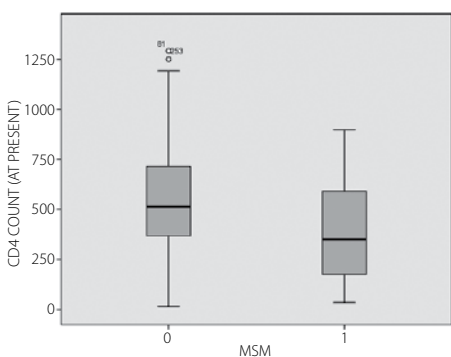
subcontinent. Involvement of other systems like neurological (16, 17), gastrointestinal (18), and hematological (19) have been extensively studied in pediatric patients, but there are few studies concerning the musculoskeletal feature among patients with HIV. This study aimed to explore the prevalence and clinical correlates of musculoskeletal manifestations in CLHIV.

## Methods

A single-center, prospective, observational study was carried out from October 2014 to September 2016 in the Regional Pediatric Anti-Retroviral Therapy (ART) Centre of a tertiary care hospital in Eastern India. The treatment and management of primary disease (HIV/AIDS) of these children were done by the State ART Centre according to WHO/NACO protocol. Children aged between 3 and 19 years, diagnosed as a case of HIV infection by Enzyme Linked immunosorbent assay (ELISA) test and/or DNA Polymerase Chain Reaction (PCR), were included with purposive sampling. Informed consent/assent (as applicable) was taken before recruitment, and the study protocol was approved by the Institutional Ethics Committee for Human Research. Children who were having musculoskeletal manifestations due to co-morbid conditions like fracture or surgery were excluded. All the children were followed up for six months.



**Figure 1.** Selection of the study population during the study period



**Figure 2.** Box-Whisker plot shows the distribution of present CD4 count with respect to presence of musculoskeletal manifestation

Data regarding disease history, present status of HIV infection, medication, and co-morbid illnesses were recorded in pre-designed proforma. Details of musculoskeletal involvement were noted. Malnutrition in these children was determined by body mass index (B.M.I.) in case of children aged >5 years, and by weight for age in case of children aged ≤5 years. A rapid screening of the musculoskeletal system was performed with the help of pediatric gait, arm, leg, spine (pGALS) screening protocol (20). At first, the study participants were shown videos of the movement that they needed to do for screening, and subsequently they were asked to imitate those movements. Following the screening examination, a more detailed examination of the relevant area, based on the “look, feel, move” principle as in the Regional Examination of the Musculoskeletal System (called REMS) was done. If any abnormality was suspected in a particular or group of joints or muscle, they were examined by X-ray, ultrasonography, relevant blood tests (complete blood count, erythrocyte sedimentation rate-ESR, C reactive protein-CRP, creatine kinase, liver function test), and serological investigations (antinuclear antibody-ANA, rheumatoid factor-RA factor). All the participants were re-examined at three- and six-month intervals. Repeat CD4 count was checked after six months. On every visit, each patient was evaluated for relevant signs and symptoms, and for growth and development monitoring.

Data were recorded on a pre-designed proforma, and were entered in Microsoft Excel 2007 spreadsheets and analyzed using IBM® SPSS® Statistics Version 22.0 (IBM Corp.; Armonk, NY, USA).  $p < 0.05$  was considered significant.

Out of 579 children infected with HIV, parents of 562 children (97.06%) consented for inclusion in our study. Eleven children died. Thirty-four children were lost to follow-up. A total of 517 children (89.29%) who had regular follow-up were included in the study (Figure 1). Baker-Wong Faces Pain Rating Scale and Visual Analogue Scale (21) were used to scale musculoskeletal pain in the age groups 3-8 years and

9-19 years, respectively. “Significant pain” was defined as >5 scoring in pain scale appropriate for that age group, and/requiring medication for relief from pain on a regular basis.

## Result

A total of 517 pediatric patients of age 3-19 years were included in the final analysis of this study. Amongst them, 59.9% belonged to the age group 9-19 years. Approximately 13.5% of the study population were aged 9 years (highest). A total of 51.8% of the evaluated children were males. Children evaluated were diagnosed at 1-16 years with a mean ( $\pm$ SD) age of diagnosis 4.317 ( $\pm$ 2.774) years, and the duration of disease in these children were from 1 to 17.5 years with a mean ( $\pm$ SD) duration of 7.301 ( $\pm$ 3.004) years (Table 1). A total of 20.9% of study population were affected by malnutrition.

The mean ( $\pm$ SD) CD4 count at diagnosis was 786.02 ( $\pm$ 251.080) cells/ $\mu$ L, while the mean ( $\pm$ SD) CD4 count at the time of evaluation was 516.81 ( $\pm$ 255.955) cells/ $\mu$ L. The distribution of CD4 count at the time of evaluation with respect to musculoskeletal manifestation is depicted in Figure 2. In the study population, 37.7% (highest among all groups) belonged to Stage 3 of W.H.O. Clinical staging system of HIV/AIDS. During assessment, around three-fourths (76.98%) of the study population was on HAART medication. Musculoskeletal manifestations were found in 11.2% children (different manifestations are depicted in Figure 3), frequent in the age group of 9-19 years ( $p=0.046$ -Fisher’s exact test) with no significant gender predilection. A lower CD4 cell count at the time of evaluation was significantly ( $p=0.008$ -Independent Mann-Whitney *U* Test) associated with presence of musculoskeletal manifestations, while no such association was found with CD4 cell count measured at the time of diagnosis of primary disease ( $p=0.381$ -Independent Mann-Whitney *U* Test).

Musculoskeletal manifestations were more common in children with a longer duration of HIV infection ( $p=0.003$ -Independent-samples

**Table 1.** Demographic attributes of the study population

	Maximum	Minimum	Std. deviation	Mean	Std error of mean
Age (in years)	19	3	3.446	9.62	0.152
Age of diagnosis (in years)	14	0.5	3.774	5.32	0.122
CD4 count at time of diagnosis ( $\mu$ L)	1951	113	251.08	786.02	11.042
CD4 count at time of evaluation ( $\mu$ L)	1293	14	255.955	516.81	11.257
WHO clinical staging	4	1	0.927	2.50	0.041
Duration of primary disease (in years)	17.5	1	3.004	7.30	0.132

**Table 2.** Different musculoskeletal manifestations in children infected with HIV with respect to age, gender, and presence of malnutrition in these children

Musculoskeletal manifestations		Gender								Total	p and Significance (Fisher's exact test)
		Female				Male					
		Malnutrition		Malnutrition		Malnutrition		Malnutrition			
3-8 years		9-19 years		3-8 years		9-19 years		3-8 years		9-19 years	
		Absent	Present	Absent	Present	Absent	Present	Absent	Present		
Non-infective articular manifestations	Absent	84	14	101	34	84	16	117	37	487	0.037* (Significant)
	Present	4	0	9	3	4	1	6	3	30	0.578** (Not Significant)
Total		88	14	110	37	88	17	123	40	517 (100%)	0.817*** (Not Significant)
Non-infective muscular manifestations	Absent	86	14	108	33	86	16	119	38	500	0.045* (Significant)
	Present	2	0	2	4	2	1	4	2	17	0.753** (Not Significant)
Total		88	14	110	37	88	17	123	40	517 (100%)	0.044*** (Significant)
Infective manifestations	Absent	87	13	107	36	87	17	120	39	506	0.538* (Not Significant)
	Present	1	1	3	1	1	0	3	1	11	0.765** (Not Significant)
Total		88	14	110	37	88	17	123	40	517 (100%)	0.706*** (Not Significant)

\*Comparison of non-infective articular manifestations between different age groups

\*\*Comparison of non-infective articular manifestations between gender

\*\*\*Comparison of non-infective articular manifestations with presence of malnutrition

\*Comparison of non-infective muscular manifestations in different age group

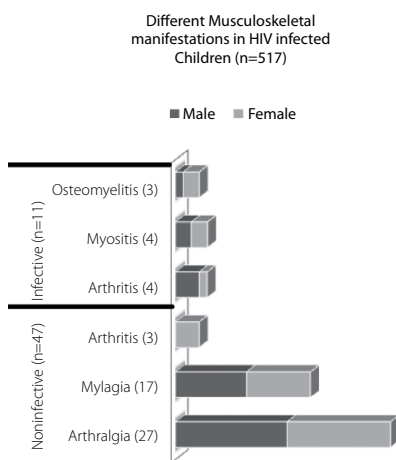
\*\*Comparison of non-infective muscular manifestations with gender

\*\*\*Comparison of non-infective muscular manifestations with presence of malnutrition

\*Comparison of infective manifestations in different age group

\*\*Comparison of infective manifestations with gender

\*\*\*Comparison of infective manifestations with presence of malnutrition



**Figure 3.** Different musculoskeletal manifestations present in the study population

median test), and in those with Stage 4 HIV infection. (p=0.009-Fisher's exact test) Also, these were found to be more frequent in children infected with HIV who are currently on HAART (p=0.013-Fisher's exact test).

Arthralgia was present in 5.22% of the study population, while myalgia occurred in 3.29%. Non-infective inflammatory arthropathies were found in 3 children (0.58%), and infective manifestations were found in 11 children, which included septic arthritis-4 (0.77%), myositis-4 (0.77%), and osteomyelitis-3 (0.58%). Presence of non-infective muscular manifestations were more common in malnourished children (p=0.044-Fisher's exact test), but there were no significant differences in infective (p=0.706-Fisher's exact test) or non-infective

articular (p=0.817-Fisher's exact test) manifestations with respect to nutritional status (Table 2).

There was no significant association between the duration of the primary disease and prevalence of non-infective musculoskeletal manifestations (p=0.177-Independent Mann-Whitney U Test); however, infective manifestations were found to be more prevalent with increased duration of disease (p=0.042-Independent Mann-Whitney U Test). A lower CD4 count at the time of evaluation was significantly associated with increased prevalence of non-infective articular manifestations (p=0.013-Independent sample median test) and infective manifestations (p=0.019-Independent sample median test). Both infective and non-infective articular and muscular manifestations were found to

be more common in the subgroup of children infected with HIV who were on anti-retroviral medications at the time of evaluation.

ANA was done in presence of arthralgia, arthritis, arthropathy, myositis, or any other manifestation suggestive of connective tissue diseases. RA factor was evaluated if arthritis or arthralgia was found. Out of 38 children, 4 showed ANA positivity (10.5%). All four were females, and belonged to the age group 9-19 years. RA factor was found in 7 of 34 children (20.6%).

## Discussion

Over the years, many studies have explored different aspects of the vulnerable children living with HIV/AIDS (CLHIV) population. But evidence on musculoskeletal manifestations in CLHIV is scarce, and most of our knowledge is built on studies done in adults (22-31). Often patients neglect the early musculoskeletal symptoms because of more extensive involvement of other systems that is also what the treating physicians are often preoccupied with. With the use of HAART as a treatment modality for the primary disease, there has been a better control of the primary disease resulting in a longer disease-free life. Therefore, while considering the long-term disease-free survival of these children in the present scenario, musculoskeletal manifestations become more and more significant. There are only a few studies worldwide on musculoskeletal manifestations involving pediatric population with HIV (10-14). One recent single-center case series from northern India has reported four children with HIV infection who developed arthritis (32). So, the index study is the first large-scale prospective study of its kind to address the spectrum of rheumatological manifestations in children infected with HIV.

Musculoskeletal manifestations were found in 11.2% of the study population, which is significantly higher than the prevalence in the general population. In an earlier study, Goodman et al. (33) concluded that musculoskeletal pain is present in 4-30% of children in a non-clinic setting, whereas a report from the Royal Children's Hospital in Melbourne found that 1.6% of the children in emergency or outpatient department had a non-traumatic muscle or joint problem (34). However, a recent study by Sabui et al. (35) reported that approximately 10.6% of healthy school-going children of foothill region of Himalayas were suffering from some form of rheumatological problems as identified by pGALS screening.

In this study, musculoskeletal manifestations were found to be more familiar in the age

group 9-19 years. This is because a child's belief about the physical nature of his/her disease greatly influences the amount of emotional distress he/she experiences and even his/her compliance to therapy.

Prevalence of musculoskeletal manifestation was found to be more in malnourished children. Also, musculoskeletal manifestations were common in advanced stage of HIV infection manifested by lower CD4 count, and in clinical Stage 4 of the disease. Most of them were currently on anti-retroviral drugs. Thus, it indicates that where the disease is extensive, rheumatological manifestations are common.

There are few notable studies with similar objectives in the general population. Munoz Fernandez et al. (36) conducted a study on 556 patients aged <30 years, with comparable results. They concluded that musculoskeletal manifestations were mainly not due to HIV infection. Rheumatological features were found in 11% of study population, whereas 11.3% of children manifested musculoskeletal problem in this study. The prevalence of arthralgia and myalgia were found to be 4.5% and 1.6% by Munoz Fernandez et al. (36), whereas in our study, 5.2% and 3.3% children had arthralgia and myalgia, respectively. *Staphylococcus aureus* was the commonest cause of infectious musculoskeletal manifestation in both the studies (60% vs. 45%).

In their 2008 study, Yao et al. (5) reported that rheumatological manifestations were present in 9% patients, with arthritis/arthralgia being the commonest (5.5%), followed by septic arthritis (1%), and osteomyelitis (0.9%) which compares well with our results.

A 1991 study by Calabrese et al. (37) evaluated 117 patients after a mean of 24.6 months, and concluded that patients with articular disease tend to have a more progressive HIV infection, and are more prone to experience progressive disease due to clinical AIDS or death. Though we could not draw such conclusion from our study due to lack of long-term follow-up, this study also found musculoskeletal manifestations to be more prevalent in advanced stages of the disease.

This study is a single-center observational study limited by the lack of long-term follow-up that might have resulted in missing some musculoskeletal manifestations in the CLHIV population over a longer time period. Also, this being a single-center study, variation in the study population from multiple centers could not be commented upon. However, to the best of our

knowledge, this study is the largest and first of its kind to explore the range of musculoskeletal manifestations, and their clinical correlates exclusively in children with HIV infection from developing country. Our study shows that a significant disease burden of musculoskeletal problems exists among the CLHIV population. Further long-term multicentric studies are imperative to get a more representative picture and to better understand the long-term outcomes.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Kolkata Medical College Ethics Committee for Human Research.

**Informed Consent:** Written informed consent was obtained from the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - R.K.M.; Design - R.K.M., T.B.; Supervision - T.B., R.K.M.; Data Collection and/or Processing - D.C., T.B.; Analysis and/or Interpretation - D.C., T.B.; Literature Search - D.C., T.B., S.B.; Writing Manuscript - D.C., T.B., S.B.; Critical Review - R.M.K., T.S.; Patient Management - T.B., R.K.M., D.C.

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**Conflict of Interest:** The authors have no conflict of interest to declare.

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