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Rheumatoid arthritis in HIV-infected individuals: a cross-sectional study in Nepal

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Abstract

Introduction: HIV is a chronic viral infection documented worldwide. It infects and destroys helper T cells (CD4), leading to a number of immunological deficiencies. The main objective of this study was to examine the rheumatoid factor (Rf) to recognize the rheumatoid arthritis prevalence rate in HIV-infected patients.

Material and methods: This hospital-based cross-sectional study was carried out among 150 HIV-positive individuals visiting ART center of Western Regional Hospital. Patients were counseled, and samples were taken. Samples were processed by MISPA-i2 and analyzed using SPSS. Rf was measured for all participants.

Results: Out of the 150 participants, 35 (23.3%) were Rf-positive for rheumatoid arthritis. In multivariable analysis, these levels were higher in 20-40 years age group, females, married, illiterate, and unknown about their HIV transmission. The prevalence of rheumatoid arthritis was observed in 23.3% of participants. Similarly, the association of sex and other variables significant values were found in education, mode of transmission, and age categories, as 0.004, 0.001, and 0.001, respectively.

Conclusions: The results of our research suggest the need for regular screening for Rf among HIV-positive patients in order to reduce mortality and pain in these individuals due to rheumatoid arthritis.

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Key words: HIV, rheumatoid arthritis, MISPA-i2, prevalence, inflammatory syndrome, AIDS.

Introduction

HIV is a chronic viral infection documented worldwide. Several immunological deficiencies are produced due to infection and destruction of helper T cells (CD4) by HIV. HIV transmission occurs mainly through blood transfusion, needle sharing among I.V. drug users, healthcare workers' exposure, and tattoo needles. Moreover, sexual contact and transplacental transmission are the main routes of HIV spread. HIV infects CD4 T cells, and persistent infection

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of cells of the monocyte from macrophages family, disrupt neurons' function. This leads to immunodeficiency and acquired immunodeficiency syndrome (AIDS) [1]. Although HIV was formerly considered to be primarily an immunosuppressive disease, mounting evidence among HIV patients on antiretroviral therapy (ART) suggest its' association with chronic inflammation and immune dysfunction, and a wide range of auto-inflammatory and auto-immune conditions have been reported in HIV-positive patients [2-4]. Similar pathological development of auto-antibodies, higher risk for chronic inflammation-driven end-organ disease, and its' relatively high baseline incidence, rheumatoid arthritis (RA) is of particular significance (range, 0.5-2% in the general population) [5-8].

There is evidence that both RA and HIV may impede HIV diagnosis (owing to false positive ELISA tests), and that HIV may obstruct RA diagnosis (via positive auto-antibodies and non-specific inflammatory arthritis) [9].

Auto-antibody overproduction and poor immunological tolerance are common characteristics of both RA and HIV: auto-antibodies, including rheumatoid factor (Rf) and anti-cyclic citrullinated peptide antibodies (anti-CCP) are both found in about 80% of RA patients [9, 10-13].

Positive Rf antibodies have been observed in the range of 10-47% in HIV patients, whereas anti-CCP antibodies were fewer; both types of auto-antibodies have a lower incidence among HIV-positive patients on antiretroviral treatment (ART) [9, 12, 13].

A positive Rf can also be caused by hepatitis C virus (HCV) infection, which is a prevalent co-infection among HIV patients. Finally, HIV has been linked to a variety of inflammatory arthritic disorders, including but not limited to RA. These conditions vary from probable HIV arthritis in 0.4-13% of HIV patients, reactive arthritis in 0-11%, and RA in 0.1-5% of HIV patients. There are no formal estimates of the RA incidence among HIV individuals when compared with uninfected cases [12, 14, 15].

Patients infected with HIV have been shown to present a higher risk of developing rheumatic diseases [16], which can occur at any stage of the disease. Moreover, HIV-positive patients with musculoskeletal involvement have reduced quality of life compared with those without rheumatic symptoms [17-21]. Association of articular syndromes with HIV include HIV-associated arthropathy, seronegative spondyloarthropathies (SPA) (reactive arthritis, psoriatic arthritis [PsA], and undifferentiated SPA), and RA [22-26].

Despite higher prognosis and longer life expectancy among HIV-positive patients, it is critical to comprehend the epidemiology and clinical aspects of RA, which is one of the most common autoimmune diseases in adults; they have yet to be documented. Furthermore, because HIV patients have underlying immunological dysfunctions, and RA is frequently treated with immunosuppression, doctors frequently struggle to manage these two dissimilar but overlapping disorders. Current RA clinical practices, therapies, and outcomes among HIV patients are little understood. Furthermore, data on the prescribing patterns, safety, and efficacy of disease-modifying anti-rheumatic medicines (DMARDs), which comprise main immunomodulatory and immunosuppressive therapies used to treat RA, are particularly limited among HIV patients [13]. In order to close these knowledge gaps, we examine Rf value in HIV-seropositive patients serologically to recognize the prevalence rates of RA in HIV-seropositive patients and the involving factors in order to increase the clinical information.

Material and methods

A cross-sectional study was designed and conducted between December 7, 2016 and January 23, 2017, to evaluate Rf values in HIV-positive patients visiting ART center of Western Regional Hospital. Ethical permission to conduct the study was obtained from the Institutional Review Committee, Pokhara University (Ref No., 110/074/75). The permission was also obtained from the Head of Department, Western Regional Hospital for sample collection from ART center. All HIV-positive patients (no bar in age and sex) visiting ART centers were included in the study, and all confirmed cases of arthritis were excluded. Written consent was obtained from each participant included in the research for details of the research work (socio-demography, status, signs, and symptoms) and privacy of their identity for distribution of the results.

In total, 150 samples were collected from the ART center of Western Regional Hospital, Ramghat, Pokhara, and processed in microbiology laboratory of the School of Health and Allied Science, Pokhara University. Serum was separated by centrifuging blood samples at 3,000 rpm for 5 min. The separated sample was transferred into well-labeled append-off tube, and stored at -20^0C.

When a sample containing Rf is added to denature human IgG, which was sensitized to latex particles, the antigen-antibody reaction occurs, leading to agglutination. The agglutination is proportional to quantity of Rf in the sample. The actual concentration is determined by interpolation from a calibration curve prepared from known value calibrators. Reagent linearity was up to 100 IU/ml. If the concentration was greater than linearity, the samples were diluted with normal saline and the assay was repeated. The result was multiplied with a dilution factor. Normal reference in serum was up to 18 IU/ml [27].

All data were analyzed using SPSS version 16.0. Frequency of incidence of different independent variables and dependent variables were calculated. Correlation between measured parameters was assessed using analytical method of Pearson's χ^2 test, and $p < 0.05$ was considered statistically significant.

Results

The present study was conducted among 150 HIV-positive individuals visiting the ART center of Western Regional Hospital. The Rf was measured in all participants, and their

Table 1. Socio-demographic characteristics of participants, *N* = 150

Variable	*n* (%)
Age (years)	
< 20	17 (11.3)
20-40	67 (44.7)
> 40	66 (44.0)
Sex	
Female	84 (56.0)
Male	66 (44.0)
Marital status	
Married	125 (83.3)
Unmarried	25 (16.7)
Mode of HIV transmission	
STD	73 (48.7)
Unknown	63 (42.0)
Vertical	14 (9.3)
Education status	
Illiterate	26 (17.3)
Literate	7 (4.7)
Primary	82 (54.7)
Secondary	35 (23.3)
CD4 count level	
< 200	13 (8.7)
200-500	60 (40.0)
> 500	77 (51.3)

medical history and socio-demographic information were also obtained. Out of the 150 participants, 35 (23.3%) were Rf-positive for RA. All the participants were provided with their test reports.

Out of the 150 participants, 17 (11.3%) were in the age group < 20 years, 67 (44.7%) were between 20 and 40 years, and 66 (44%) participants were > 40 years old. In total, 84 (56%) females and 66 (44%) males were included in our study. 13 (8.7%) participants had CD4 count less than 200, 60 (40%) had between 200 and 500, and 77 (51.3%) had above 500. Our study included 125 (83.3%) married and 25 (16.7%) unmarried individuals. Similarly, 82 (54.7%) were primary school educated, 35 (23.3%) were secondary school educated, 7 (4.7%) were bachelor and above, and 26 (17.3%) were illiterate. Mode of transmission was also analyzed as per the information given by the participants. According to them, 73 (48.7%) were infected with HIV through sexual transmission (STD), 14 (9.3%) via vertical transmission, and 63 (42%) did not know about their way of transmission, as shown Table 1. Furthermore, Rf was evaluated to identify the status of RA in HIV participants and was observed during the study, as demonstrated in Table 2. 115 (76.7%) patients were Rf-negative, and 35 (23.3%) were Rf-positive, which revealed RA.

Table 2. Rheumatoid factor for rheumatoid arthritis status of participants, *N* = 150

Rheumatoid factor	*n* (%)
Negative	115 (76.7)
Positive	35 (23.3)

Out of the 35 Rf-positive for RA cases, age-wise prevalence was the highest in the 20-40 years age group (12.0%) compared with the 40 years age group (8.0%), and was the lowest in the less than 20 years age group (3.3%). The prevalence was the highest in females (*n* = 21, 14%) compared with males (*n* = 14, 9.3%). Individuals with CD4 count > 500 were more prevalent (*n* = 21, 14%). Similarly, the prevalence was the highest in people living inside of Kaski (*n* = 19, 12.7%) compared with people living outside of Kaski. Participants who were married showed the highest prevalence (*n* = 27, 8%) than unmarried (*n* = 8, 5.3%). Likewise, the prevalence was the highest in individuals with primary education, as shown Table 3.

The association of sex with other variables were also examined in our study. Out of 150 participants, a significant value was found in education, mode of transmission, and age categories as 0.004, 0.001, and 0.001, respectively, showing significant values (Table 4). In the association of age with sex, the highest number of participants was seen in females, with total of 84 (56.0%), the highest in the age group of 20-40 years, with 47 female participants (31.3%), and 66 males (44.0%) as the lowest, with significant *p*-value of 0.005 (Table 5). In the association of age with CD4 count status, the highest was seen in the participants with more than 500 CD4 counts (*n* = 77, 51.3%), the highest in the age group of 20-40 years (*n* = 37, 24.7%), and the lowest in 13 individuals (8.7%) with less than 200 CD4 counts, with significant *p*-value of 0.005 (Table 6). In the association of age with education status of HIV people, the highest number of participants was seen among people with primary education (*n* = 82, 54.7%), the highest in the age group of 20-40 years (*n* = 36, 24.0%), and the lowest number was noted among literate people (*n* = 7, 4.7%), with highly significant *p*-value of 0.003 (Table 7).

Discussion

In the present study, 150 HIV-positive individuals were analyzed for Rf, and among them, a significantly high prevalence of Rf was found (*n* = 35, 23.3%). Out of the 35 Rf-positive individuals, the highest prevalence was in the age group of 20-40 years (12.0%) compared with over 40 years of age group (8.0%), while the lowest prevalence was observed in the age group of less than 20 years (3.3%). The prevalence was the highest in female participants (*n* = 21, 14.0%) compared with their males' counterparts (*n* = 14, 9.3%).

Table 3. Association of rheumatoid factor (Rf) with socio-demographic characteristics of participants

Variable	Rf, *n* (%)		Total, *n* (%)	χ^2 value	*p*-value
	Negative	Positive			
Age (years)					
< 20	12 (8.0)	5 (3.3)	17 (11.3)	1.798	0.407
20-40	49 (32.7)	18 (12.0)	67 (44.7)		
> 40	54 (36.0)	12 (8.0)	66 (44.0)		
Total	115 (76.7)	35 (23.3)	150 (100.0)		
Sex					
Female	63 (42.0)	21 (14.0)	84 (56.0)	0.296	0.586
Male	52 (34.7)	14 (9.3)	66 (44.0)		
Total	115 (76.7)	35 (23.3)	150 (100.0)		
Place of residence					
Baglung	4 (2.7)	0 (0.0)	4 (2.7)	11.491	0.070
Gorkha	2 (1.3)	0 (0.0)	2 (1.3)		
Kaski	69 (46.0)	19 (12.7)	88 (58.7)		
Lamjung	3 (2.0)	0 (0.0)	3 (2.0)		
Myagdi	6 (4.0)	2 (1.3)	8 (5.3)		
Parbat	11 (7.3)	4 (2.7)	15 (10.0)		
Syangja	8 (5.3)	0 (0.0)	8 (5.3)		
Tanhu	12 (8.0)	10 (6.7)	22 (14.7)		
Total	115 (76.7)	35 (23.3)	150 (100.0)		
Marital status					
Married	98 (65.3)	27 (18.0)	125 (83.3)	1.260	0.262
Unmarried	17 (11.3)	8 (5.3)	25 (16.7)		
Total	115 (76.7)	35 (23.3)	150 (100.0)		
Mode of HIV transmission					
STD	55 (36.7)	18 (12.0)	73 (48.7)	1.918	0.383
Unknown	51 (34.0)	12 (8.0)	63 (42.0)		
Vertical	9 (6.0)	5 (3.3)	14 (9.3)		
Total	115 (76.7)	35 (23.3)	150 (100.0)		
Education level					
Illiterate	18 (12.0)	8 (5.3)	26 (17.3)	1.925	0.604
Literate	6 (4.0)	1 (0.7)	7 (4.7)		
Primary	62 (41.3)	20 (13.3)	82 (54.7)		
Secondary	29 (19.3)	6 (4.0)	35 (23.3)		
Total	115 (76.7)	35 (23.3)	150 (100.0)		
CD4 count level					
< 200	12 (8.0)	1 (0.7)	13 (8.7)	2.539	0.229
200-500	47 (31.3)	13 (8.7)	60 (40.0)		
> 500	56 (37.3)	21 (14.0)	77 (51.3)		
Total	115 (76.7)	35 (23.3)	150 (100.0)		

The prevalence of Rf in HIV-positive individuals was more in our study (23.3%) than in a study done among non-HIV infected individuals, i.e., Chopra *et al.*, with 3.5% [28], Mahajan *et al.*, with 2.9% [29], Joshi *et al.*, with 0.45% [30], Malaviyaet *et al.*, with 0.7% [31], and Kar *et al.*, with 5.2% [32]. While no higher prevalence was found in

Table 4. Association of sex with other variables of participants

Variable	Sex, *n* (%)		Total, *n* (%)	χ^2 value	*p*-value
	Female	Male			
Age (years)					
< 20	9 (6.0)	8 (5.3)	17 (11.3)	10.445	0.004
20-40	47 (31.3)	20 (13.3)	67 (44.6)		
> 40	28 (18.7)	38 (25.3)	66 (44.0)		
Total	84 (56.0)	66 (44.0)	150 (100.0)		
Marital status					
Married	73 (48.7)	52 (34.7)	125 (83.3)	1.753	0.270
Unmarried	11 (7.3)	14 (9.3)	25 (16.7)		
Total	84 (56.0)	66 (44.0)	150 (100.0)		
Mode of HIV transmission					
STD	52 (34.7)	21 (14.0)	73 (48.7)	13.887	0.001
Unknown	25 (16.7)	38 (25.3)	63 (42.0)		
Vertical	7 (4.7)	7 (4.7)	14 (9.3)		
Total	84 (56.0)	66 (44.0)	150 (100.0)		
Education level					
Illiterate	19 (12.7)	7 (4.7)	26 (17.3)	13.959	0.001
Literate	0 (0.0)	7 (4.7)	7 (4.7)		
Primary	49 (32.7)	33 (22.0)	82 (54.7)		
Secondary	16 (10.7)	19 (12.7)	35 (23.3)		
Total	84 (56.0)	66 (44.0)	150 (100.0)		

Table 5. Association of age with sex of participants

Sex	Age (years), *n* (%)			Total	χ^2 value	*p*-value
	< 20	20-40	> 40			
Female	9 (6.0)	47 (31.3)	28 (18.7)	84 (56.0)	10.445	0.005
Male	8 (5.3)	20 (13.3)	38 (25.3)	66 (44.0)		
Total	17 (11.3)	67 (44.7)	66 (44.0)	150 (100.0)		

Table 6. Association of age with CD4 count of participants

Level of CD4	Age (years), *n* (%)			Total	χ^2 value	*p*-value
	< 20	20-40	> 40			
< 200	0 (0.0)	7 (4.7)	6 (4.0)	13 (8.7)	11.799	0.005
200-500	3 (2.0)	23 (15.3)	34 (22.7)	60 (40.0)		
> 500	14 (9.3)	37 (24.7)	26 (17.3)	77 (51.3)		
Total	17 (11.3)	67 (44.7)	66 (44.0)	150 (100.0)		

non-HIV individuals as in line with the current research. In studies done among HIV individuals, less prevalence was found in Mahajan *et al.*, with 11.8% [33], Fernandez *et al.*, with 11% [34], Berman *et al.*, with 7.8% [35], Yao *et al.*, with 9% [36], and Chinniahet *et al.*, with 22% [21, 37], which is nearly the same as in our study, whereas less prevalence than shown by Kaddu-Mukasa *et al.*, with 27% [38]. This higher prevalence rate may be due to living in developing country and lack of health education, which may lead to more infection and inflammation, leading to joint pain. Age-wise prevalence was the highest in the age group of 20-40 years (12.0%) compared with the over 40 years

Table 7. Association of age with education of participants

Education level	Age (years), *n* (%)			Total	χ^2 value	*p*-value
	< 20	20-40	> 40			
Illiterate	1 (0.7)	6 (4.0)	19 (12.7)	26 (17.3)	19.510	0.003
Literate	0 (0.0)	2 (1.3)	5 (3.3)	7 (4.7)		
Primary	13 (8.7)	36 (24.0)	33 (22.0)	82 (54.7)		
Secondary	3 (2.0)	23 (15.3)	9 (6.0)	35 (23.3)		
Total	17 (11.3)	67 (44.7)	66 (44.0)	150 (100.0)		

age group (8.0%), and the lowest in the age group of less than 20 years (3.3%). This may be due to the highly active age group, which leads to progressively more infections as well as rheumatoid conditions, which is similar to a study of Mahajan *et al*., with 11.8% [33] and Fernandez *et al*., with 11% [34].

Prevalence was the highest in females (*n* = 21, 14.0%) compared with their males' counterparts (*n* = 14, 9.3%), which is similar to a study by Fernandez *et al*., with 11% [34], Berman *et al*., with 7.8% [35], Yao *et al*., with 9% [36], and Chinniah *et al*., with 22% [37, 39]. Individuals with CD4 count > 500 were more prevalent (*n* = 21, 14.0%), which shows that CD4 count has no role in RA occurrence. Similarly, the prevalence was the highest in people living inside of Kaski (*n* = 19, 12.7%) than people living outside of Kaski. Moreover, participants who were married showed the highest prevalence (*n* = 27, 8.0%) compared with unmarried individuals (*n* = 8, 5.3%).

Conclusions

Even though all patients visiting ART center are receiving antiretroviral therapy, still, the prevalence of RA in these patients was found high. RA was noted more frequent among females than males. The result of our research suggests the need for regular screening of patients for Rf to detect RA, so that it can help in reducing mortality of HIV-infected individuals due to arthritis.

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Conflict of interest

The authors declare no conflict of interest.

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