Effect of Human Immunodeficiency Virus Infection on Disease Activity in Rheumatoid Arthritis: A Retrospective Study in South Africans

Gareth Tarr, Mohamed Makda, Eustasius Musenge, and Mohammed Tikly

ABSTRACT. ***Objective.*** To determine the effect of human immunodeficiency virus (HIV) infection on disease activity in rheumatoid arthritis (RA).

Methods. A retrospective records review of patients who contracted HIV infection subsequent to RA diagnosis (HIV group), compared to an HIV-negative group of patients with RA (control group), for 28-joint Disease Activity Score (DAS28) scores at initial presentation (T0) and last clinic visit (TL), and at diagnosis of HIV infection (TH) in the HIV group.

Results. Of 1712 patients with RA, 85 were HIV-positive (4.9%), 43 of them contracting HIV subsequent to RA diagnosis. The mean (SD) age, RA disease duration, and duration following diagnosis of HIV were 47.1 (10.1), 10.5 (8.4), and 2.9 (2.0) years, respectively, for the HIV group. Both the HIV and control groups showed similar improvement in joint counts and C-reactive protein (CRP) at visit TL, in spite of methotrexate (MTX) being withdrawn in most patients in the HIV group by visit TL (11.6% in the HIV group were still taking MTX vs 83.7% in the control group, $p = 0.0002$), but a minority (13.9%) had ongoing moderate to high disease activity at visit TL. In the HIV group, the mean DAS28-erythrocyte sedimentation rate (ESR) and DAS28-CRP scores were similar at baseline, but at visits TH and TL the mean DAS28-ESR scores were significantly higher than the mean DAS28-CRP scores (31% and 31.8%, $p < 0.0005$ and $p < 0.004$, respectively), mainly resulting from ESR increase following HIV seroconversion.

Conclusion. Disease activity improved in most patients in the HIV group in spite of stopping the MTX as the "anchor drug." The DAS28-ESR overestimates disease activity compared to the DAS28-CRP in the setting of HIV infection. (J Rheumatol First Release July 15 2014; doi:10.3899/jrheum.130896)

Key Indexing Terms:
RHEUMATOID ARTHRITIS HUMAN IMMUNODEFICIENCY VIRUS COMORBIDITY

Human immunodeficiency virus (HIV) infection carries a major health burden in South Africa. In the Gauteng Province, the estimated prevalence of HIV infection is 10.3%. It is highest among females aged 25–29 years at 32.7% and males 30-34 years at 25.8%[1]. In such a setting, patients with chronic medical conditions such as rheumatoid arthritis (RA), not unexpectedly, occasionally acquire HIV infection.

The interaction between RA and HIV infection can be viewed at a number of levels. First, RA is mainly a Th1-driven immune disorder, whereas HIV infection causes destruction of CD4 T cells. Not surprisingly, a number of earlier anecdotal case reports, mainly from North America, have shown that HIV infection is associated with improvement in RA disease activity[2,3,4]. Second, HIV infection is associated with a nonspecific hypergammaglobulinemia, which results in an increase in erythrocyte sedimentation rate (ESR), even in the absence of active bacterial infection or inflammation[5]. Third, in the presence of HIV infection, immunosuppressive agents, particularly methotrexate (MTX), may increase the risk of opportunistic infections[6].

Because to our knowledge there are no published longitudinal studies on the effect of HIV infection on RA disease activity, particularly in sub-Saharan Africa, we undertook a retrospective study of disease activity, before and after HIV seroconversion, in patients with RA.

MATERIALS AND METHODS

Case records were reviewed of patients 18 years and older attending the Arthritis Clinic, Chris Hani Baragwanath Academic Hospital, fulfilling the American College of Rheumatology 1987 classification criteria of RA[7], who were HIV-negative at the time of RA diagnosis and who subsequently contracted HIV infection. Patients were screened annually for HIV infection, irrespective of symptoms. The HIV diagnosis was based on at least 2 consecutive positive HIV ELISA tests. Disease activity and drug

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therapy were compared to a control group of HIV-uninfected patients with RA attending the same clinic, matched on a 1:1 basis and for sex, age (± 5 yrs), and disease activity. The groups were matched for disease duration (± 2 yrs) to time to HIV diagnosis for the HIV group and total disease duration for the control group.

Disease activity variables were documented at the timepoints RA diagnosis (T0) and at last clinic visit (TL) for both groups, and additional visit closest to HIV diagnosis (TH) for the HIV group. These variables included the 28-joint swollen and tender joint counts, patient global assessment (PGA), ESR, and C-reactive protein (CRP), from which the composite disease activity scores DAS28-ESR and DAS28-CRP were calculated. Also documented were rheumatoid factor status, therapy with disease-modifying antirheumatic drugs (DMARD; particularly MTX), and where available, the peripheral CD4 counts. Because of the paucity of published data regarding the safety of MTX with HIV infection, the general policy in our unit has been to stop MTX following HIV seroconversion, especially when the CD4 count is < 500 cells/ml. However, in some instances MTX was continued at the discretion of the treating rheumatologist(s).

Statistical methods. Data was captured on Microsoft Excel and analyzed using GraphPad and Statistica software. The unpaired Student's t test was used to compare continuous variables and Yates' corrected chi-square test or the 2-tailed Fisher's exact test to compare categorical variables. The Pearson's correlation test was applied to test for correlations between continuous variables. A p value of < 0.05 was considered significant.

RESULTS

Of the 1712 records of patients with RA that were reviewed, 85 patients (4.9%) tested positive for HIV infection, of whom 43 (39 females and 4 males) contracted the infection after the diagnosis of RA was made. Only data for the latter group, called the HIV group, were included in the analysis. The mean (SD) age, RA disease duration, and duration following the diagnosis of HIV were 47.1 (10.1), 10.5 (8.4), and 2.9 (2.0) years, respectively (Table 1). The disease duration to HIV diagnosis, visit TH for the HIV group, and to visit TL for the control group, were not significantly different. As shown in Table 2, the HIV group had a significant improvement in all measurements of disease activity, with the exception of ESR, from visits T0 to TH, and was sustained or showing further improvement through to visit TL, a mean (SD) duration of 2.9 (2.0) years from visit TH. The control group showed a similar fall in markers of disease activity, including the mean ESR, from visits T0 to TL (Table 2). The disease activity variables at visit TL were similar between the groups, except that the HIV group had a better mean PGA (p = 0.013) and a higher mean ESR (p < 0.0001).

Table 1. Demographics and rheumatoid serology of the human immunodeficiency virus (HIV) and control groups.

Characteristics	HIV Group, n = 43	Control Group, n = 43	p
Age, yrs, mean (SD)	47.1 (10.1)	45.7 (8.0)	NS
Mean (SD) age at RA diagnosis, yrs	36.4 (12.1)	38.5 (8.0)	NS
Mean (SD) total RA disease duration, yrs	10.5 (8.5)	7.1 (3.8)	0.02
Mean (SD) HIV disease duration, yrs	2.9 (2.0)	—	—
Female: Male	39:4	40:3	
RF (%)	38 (88)	32 (74)	NS

NS: not significant; RA: rheumatoid arthritis; RF: rheumatoid factor.

The clinical improvement in the HIV group occurred in spite of the majority of patients discontinuing MTX following the diagnosis of HIV infection, such that only 5 patients (11.6%) were taking MTX at visit TL, compared with 36 patients (83.7%) in the control group (p < 0.00001; Table 2). In the remaining 29 of 34 patients in the HIV group in whom MTX was prescribed before the diagnosis of HIV infection, the drug was substituted with sulfasalazine (SSZ) and/or chloroquine (CQ). The proportion of patients taking SSZ at visit TL was higher in the HIV group compared to the control group (62.7% vs 32.5%, p = 0.02), but there was no significant difference in CQ and oral prednisone use.

In the HIV group, the mean DAS28-ESR and DAS28-CRP scores were similar at visit T0, but following HIV seroconversion, the nonspecific increase in ESR resulted in divergence between the mean DAS28-ESR and DAS28-CRP scores such that the former was significantly higher at visit TH (26.9%, p = 0.0005) and at visit TL (31.8%, p = 0.004; Table 2). This is evident in Figure 1, where in the case of the HIV group there was a divergence from T0 to TH between the mean DAS28-ESR and DAS28-CRP scores, but the 2 lines paralleled each other from TH to TL.

Consequently, a significantly larger proportion of patients were in disease remission, defined as a DAS28 ≤ 2.6, by the DAS28-CRP than the DAS28-ESR (32/43 vs 11/43, respectively, p = 0.001) at visit TL. In the case of the control group, the mean DAS28-ESR and DAS28-CRP scores did not differ significantly at visits T0 and TL and the proportions of patients in disease remission were similar by the 2 scoring methods at TL (Table 2 and Figure 1).

In the HIV group, excluding patients initiated on highly active antiretroviral therapy (HAART), the mean (SD) peripheral CD4 counts at visit TH and TL were 414.7 (201.2) and 390.7 (293.7) cells/ml, respectively. There were no significant correlations between the peripheral CD4 counts and DAS28 scores or individual disease activity variables; neither did the CD4 count predict disease remission. In the subgroup of 6 patients in whom HAART was initiated, the mean (SD) DAS28-CRP at visits T0, TH, and TL were 5.16 (0.5), 2.86 (1.6), and 2.08 (0.8), respectively, significantly better at visits TH compared to T0 (p = 0.006), but no significant change between TH and TL.

DISCUSSION

The female-to-male ratio in the HIV-positive group of 9:1 is higher than the 5:1 reported previously in RA in this population[8]. These findings again highlight the burden of HIV being disproportionately higher in South African women[1]. The 4.9% prevalence of HIV infection in the total RA cohort in our present study is lower than the estimated general

Table 2. Disease activity variables, expressed as mean (SD) over time, in the human immunodeficiency virus (HIV) and control groups.

Variable	HIV Group, n = 43					Control Group, n = 43		
	T0	TH	p*	TL	p**	T0	TL	p*
SJC	5.5 (4.3)	0.9 (1.8)	< 0.0001	0.6 (1.7)	NS	5.1 (3.6)	1.2 (1.5)	< 0.0001
TJC	8.1 (5.3)	2.0 (4.1)	< 0.0001	0.8 (2.3)	NS	7.2 (6.0)	1.6 (2.8)	< 0.0001
Patient global assessment, mm	52.4 (22.9)	24.4 (19.8)	< 0.0001	15.5 (17.4)	0.04	50.0 (16.3)	27.3 (18.7)	< 0.0001
ESR, mm/h	41.7 (25.4)	47.0 (30.7)	NS	50.5 (34.7)	NS	41.2 (28.2)	24.4 (15.2)	0.0016
CRP, mg/dl	37.1 (40.1)	12.6 (15.8)	0.002	12.3 (12.0)	NS	34.2 (44.9)	13.4 (12.9)	0.014
DAS28-ESR	5.2 (1.3)	3.4 (0.9)	< 0.0001	2.9 (0.9)	0.01	5.1 (1.1)	3.1 (1.0)	< 0.0001
DAS28-CRP	4.9 (1.1)	2.6 (1.0)	< 0.0001	2.2 (0.8)	0.02	4.7 (1.0)	2.8 (1.0)	< 0.0001
DAS28-CRP ≤ 2.6 (%)	2 (4.7)	23 (53.5)	< 0.0001	32 (74.4)	0.07	1 (2.3)	23 (53.5)	< 0.0001
Percent difference between DAS28-ESR and DAS28-CRP	6.1%	31%	—	31.8%	—	8.5%	10.1%	—
p value	NS	0.0005	—	0.004	—	NS	NS	—
Methotrexate (%)	20 (46.5)	34 (79)	0.004	5 (11.6)	< 0.001	19 (44.2)	36 (83.7)	0.001
Sulfasalazine (%)	19 (44.2)	18 (42.0)	NS	27 (62.8)	NS	14 (33.0)	14 (33.0)	NS
Chloroquine (%)	6 (14.0)	19 (44.2)	0.04	28 (65.1)	NS	11 (25.6)	25 (58.4)	0.005
Prednisone ≤ 7.5 mg (%)	13 (30.2)	7 (16.3)	NS	10 (23.3)	NS	16 (37.2)	7 (16.3)	NS

*T0 vs TH. ** TH vs TL. T0: initial RA diagnosis; TH: at HIV diagnosis; TL: at last clinic visit; SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score; NS: not significant.

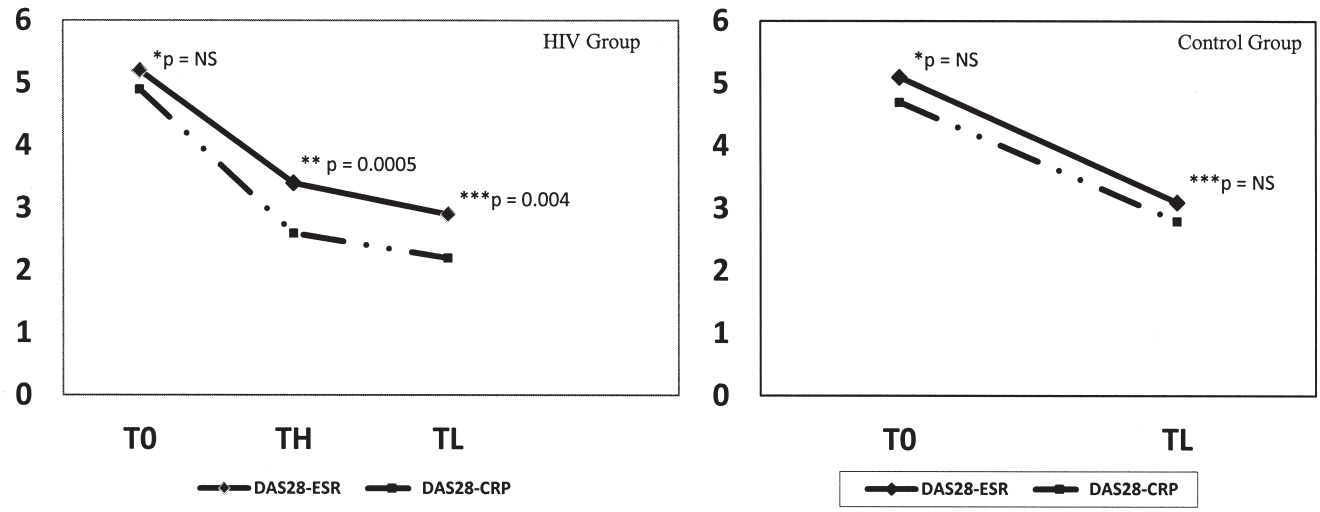

Figure 1. Changes in 28-joint Disease Activity Scores (DAS28) in the human immunodeficiency virus (HIV) and control groups over time. *T0 DAS28-ESR vs DAS28-CRP. **TH DAS28-ESR vs DAS28-CRP. ***TL DAS28-ESR vs DAS28-CRP. NS: not significant; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; T0: initial rheumatoid arthritis diagnosis; TH: at HIV diagnosis; TL: at last clinic visit.

population prevalence of 10.3% and substantially lower than the 32.7% estimated prevalence in women 25–29 years[1]. A possible explanation is that the patients with RA were less sexually active because they were older and polyarticular joint disease imposed physical limitations.

Our findings support the notion that HIV infection improves RA disease activity in most cases. Moreover, this improvement is sustained long after withdrawal of the "anchor" DMARD, MTX. Despite there being a significantly higher number of patients in the control group taking MTX therapy at visit TL, the HIV group fared significantly better in the PGA, a trend toward lower overall mean DAS28-CRP score and numerically greater proportion of patients achieving disease remission compared to the control group (74.4% vs 53.4%), although not statistically significant. The reduction in disease activity between visits T0 and TH in the HIV group is mostly an MTX effect, but cannot exclude a component from HIV because the HIV infection is likely to have been acquired several months before visit TH, given the relatively low CD4 count at this point. Thereafter the "HIV effect" on disease activity dominates, although it is plausible that in some patients

there was sustained clinical improvement because of the residual effect of MTX and addition of SSZ and/or CQ.

There was no clear relationship between the CD4 count and decline in RA disease activity following detection of HIV infection. The CD4 count was moderately reduced at the time of diagnosis of HIV infection, and it would seem that improvement in rheumatoid disease activity is linked to a fairly modest lowering in the CD4 count. Studies with anti-CD4 agents have shown only modest improvement in disease activity[9]. The CD4 counts in most patients were not at a level where opportunistic infections (< 350 cells/ml) or AIDS-related disorders (< 200 cells/ml) supervene. The pathophysiology of RA and HIV is complicated, and why some patients have ongoing joint inflammation despite being immunosuppressed provides support for work regarding T cell independent inflammation in RA[10]. Conversely, no significant increase in disease activity was noted in the 6 patients who commenced HAART. However, there have been isolated case reports of RA disease flares occurring on commencing HAART, possibly as part of an immune reconstitution[11].

In both the control and HIV groups, all clinical variables improved with time, except the ESR following HIV seroconversion in the HIV group, which had an upward trend from visits T0 to TL. As a result, despite overall improvement in disease activity in both groups, whether measured by DAS28-CRP or DAS28-ESR, the DAS28-ESR overestimated disease compared to the DAS-CRP by more than 30% at visit TL in the HIV group. That DAS28-ESR overestimates disease activity has been documented previously in the absence of HIV infection, but the mean difference between the 2 scoring methods was much smaller and mainly related to long disease duration in a large Japanese study[12]. Our findings thus suggest that in the presence of HIV infection, the DAS28-ESR is not a reliable measure of overall RA disease activity. The ESR is frequently elevated with HIV infection in the absence of bacterial infection. Arango, *et al*, in a study of HIV-positive children with acute infection, showed that while the CRP normalized with recovery from acute infection, the ESR remained elevated[13]. One explanation for the persistent elevation of the ESR in HIV infection is the hypergammaglobulinemia related to an increase in the antiinflammatory cytokines interleukin 4 (IL-4) and IL-10, upregulated humoral immunity, and the production of immunoglobulins, specifically increases in IgA, IgM, and β2-microglobulin[14].

Being a retrospective study, one of the main limitations was incomplete data for some of the variables. In particular, data for the CD4 cell counts and HIV viral load counts were missing for many patients and hence we were not able to assess the relationship of disease activity with the severity of HIV infection with certainty. Too few of our patients were taking HAART to comment on disease activity response to improving immune status. Another limitation is that the joint counts were done by clinicians of varying experience, which may have affected the DAS28 scores. We were unable to assess the relationship of gammaglobulin levels with the ESR, because there were insufficient data to compare pre-HIV and post-HIV gammaglobulin levels.

In spite of these limitations, our results indicate that patients who contract HIV infection after the diagnosis of RA show overall improvement in disease activity. This improvement was sustained even after withdrawal of MTX treatment. Our findings also show that DAS28-ESR is a less reliable measure of disease activity than the DAS28-CRP because of the nonspecific increase in ESR with HIV infection. In spite of the overall improvement in disease activity, patients with ongoing disease activity still have unmet needs, especially with respect to the safety of MTX. Prospective studies are needed to determine the relationship of the CD4 cell count and viral load to RA disease activity, the effect of HAART on overall disease activity in RA, and more specifically, the ESR. The safety of MTX in HIV infection also needs further study.

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REFERENCES

1. Rehle TM, Hallett TB, Shisana O, Pillay-van Wyk V, Zuma K, Carrara H, et al. A decline in new HIV infections in South Africa: estimating HIV incidence from three national HIV surveys in 2002, 2005 and 2008. PLoS One 2010;5:e11094.
2. Calabrese LH, Wilke WS, Perkins AD, Tubbs RR. Rheumatoid arthritis complicated by infection with the human immunodeficiency virus and the development of Sjogren's syndrome. Arthritis Rheum 1989;32:1453-7.
3. Bijlsma JW, Derksen RW, Huber-Bruning O, Borleffs JC. Does AIDS 'cure' rheumatoid arthritis? Ann Rheum Dis 1988;47:350-1.
4. Lapadula G, Iannone F, Zuccaro C, Covelli M, Grattagliano V, Pipitone V. Recovery of erosive rheumatoid arthritis after human immunodeficiency virus-1 infection and hemiplegia. J Rheumatol 1997;24:747-51.
5. Ndakotsu MA, Salawu L, Durosinmi MA. Relation between erythrocyte sedimentation rate, clinical and immune status in HIV-infected patients. Niger J Med 2009;18:208-10.
6. Tikly M. The scourge of HIV infection in sub-Saharan Africa — a rheumatological perspective. J Rheumatol 2011;38:973-4.
7. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
8. Tikly M, Zannettou N, Hopley M. A longitudinal study of rheumatoid arthritis in South Africans. MedGenMed 2003;5:2.
9. Scheerens H, Su Z, Irving B, Townsend MJ, Zheng Y, Stefanich E, et al. MTRX1011A, a humanized anti-CD4 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a Phase I randomized, double-blind, placebo-controlled study incorporating pharmacodynamic biomarker assessments. Arthritis Res Ther 2011;13:R177.
10. Black A, Madhok R. The coexistence of classic RA and AIDS. J Rheumatol 1992;19:1484-5.

11. Azeroual A, Harmouche H, Benjilali L, Mezalek ZT, Adnaoui M, Aouni M, et al. Rheumatoid arthritis associated to HIV infection. Eur J Intern Med 2008;19:e34-5.
12. Matsui T, Kuga Y, Kaneko A, Nishino J, Eto Y, Chiba N, et al. Disease Activity Score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients in Japan. Ann Rheum Dis 2007;66:1221-6.
13. Arango CA, Midani S, Alvarez A, Kubilis PS, Rathore MH. Usefulness of acute phase reactants in the diagnosis of acute infections in HIV-infected children. South Med J 1999;92:209-13.
14. Schwartlander B, Bek B, Skarabis H, Koch J, Burkowitz J, Koch MA. Improvement of the predictive value of CD4+ lymphocyte count by beta 2-microglobulin, immunoglobulin A and erythrocyte sedimentation rate. The Multicentre Cohort Study Group. Aids 1993;7:813-21.