

Clinical and Laboratory Predictors of Articular Disorders Among HIV-infected Patients Seen at Teaching Hospital Southeast Nigeria

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Abstract

Background: HIV infection may be associated with different arthropathies that are often underdiagnosed. There is also paucity of reported studies of relationship between clinical and laboratory features of HIV-infected patients and articular disorders. **Aims:** To determine the predictors of articular disorders among HIV-infected patients seen at tertiary hospital Nigeria. **Subjects and Methods:** Hospital-based cross-sectional descriptive study. Subjects were recruited from outpatient clinics of the study centers. Persons aged 16 years and above were recruited via stratified sampling method. Subjects with trauma, degenerative arthritis, malignancy, hepatitis B surface antigen and anti-hepatitis C virus positivity or previously known to have pulmonary tuberculosis or rheumatological disorders were excluded. Pretest-improved semi-structured questionnaire was administered to the recruited 480 subjects comprising 240 HIV positive subjects (HPS) and 240 HIV-negative subjects (HNS). Blood for relevant laboratory tests and radiographs were done where necessary. Diagnosis of articular disorder was based on American College of Rheumatology and European Spondyloarthropathy Study Group classification guidelines. Statistical Package for Social Sciences version 15 (SPSS Inc., Chicago, IL, USA) was used for data entry, validation, and analysis. **Results:** Of the 480 participants, both HPS and HNS were made up of 95 males and 145 females. There was statistically significant difference between the frequency of occurrence of articular disorders among the HPS of 37.1% (89/240) and the HIV-negative controls of 16.2% (39/240) ($\chi^2 = 26.63$ $P < 0.01$). Arthralgia frequency of 29.6% (71/240), HIV-associated arthritis 4.6%, (11/240) (Reiter's disease 1.3% (3/240), undifferentiated spondyloarthropathy 1.3%, (3/240) and gout 0.4% (1/240) (were seen among the HPS. Only arthralgia was found among HNS. Erythrocyte sedimentation rate (ESR) and age were the best predictors of arthralgia presence. CD4+ T-cell count was predictive of HIV-associated arthritis. **Conclusions:** Articular disorders are commoner among HIV patients than HNS. ESR and age were the best predictors of Arthralgia presence among HIV-infected patients. CD4+ T-cell count was predictive of HIV-associated arthritis.

Keywords: Articular disorders, HIV, Predictors, Southeast Nigeria

Introduction

HIV infection may be associated with different arthropathies that are often underdiagnosed.^[1-8] These articular

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conditions (arthralgia, arthritis, and spondyloarthropathy) are either caused by the HIV infection itself, antiretroviral therapy, adaptive changes in the immune system or are secondary to microbial infections. There is paucity of reported studies of articular disorders among HIV-positive subjects (HPS) in Nigeria. There is also paucity of reported studies of relationship between clinical and laboratory features of HIV-infected patients and articular disorders. This study was embarked on to determine the predictors of articular disorders among HIV-infected patients seen at a tertiary institution in South East Nigeria.

Hypothesis

The erythrocyte sedimentation rate (ESR), duration of highly active antiretroviral therapy (HAART), age, CD4+ T-cell count, and viral load of the HPS are predictors of articular disorders among HPS.

Subjects and Methods

The study was a hospital based cross-sectional descriptive study. It was conducted at a Tertiary Health Institution in South East Nigeria. The HPS were recruited from the GOPD and special HIV clinics of the study center, and the controls from the Voluntary Confidential Counseling and Testing Centers. The recruitment of subjects for the study took place from August 3, 2011 to May 28, 2012. The study population was largely Igbo tribe. Ethical approval was obtained from the Ethics and Research Committee of the Tertiary Health Institution. Also, permission to use the HIV laboratory services and data repository was sought and obtained from the Harvard School of Public Health (President's Emergency Plan for AIDS Relief) Boston USA (The sponsor of the HIV/ARV Clinic). The provisions of Helsinki Declaration were observed.

The sample size (n) was determined using the WHO formula^[9] for calculating the minimum sample size from an infinite population and prevalence rate of articular disorders among HIV patients in Kenya of 17%.^[10] Thus $n = 216$ rounding up by 10%, for higher accuracy appropriate sample size = 240 HPS. The control was: 240 HIV-negative subjects (HNS). These gave a total of 480 subjects for the study.

Subjects were recruited by systematic random sampling of all the HPS attending the clinics of the tertiary health institution hospitals. Every third HPS attending the clinics was recruited if he or she was eligible and gave consent. Those that were not eligible or declined consent were dropped and the systematic sampling continued until the sample size was completed. The HPS was matched gender and age group wise with the control. A pretest questionnaire was administered to 30 HIV-positive and 30 HIV-negative subjects who were recruited randomly from the eligible participants to assess performance and applicability of the semi-structured questionnaire for detection

of articular disorders. Observations made were used to improve on the semi-structured questionnaire, but the subjects for the pretest were however excluded from the main study.

The pretest-improved semi-structured researcher administered questionnaire was applied to the study population. It was used to assess the symptoms and the signs of articular disorders and tests results. The researcher administered questionnaire had sections containing examination based on the gait, arms, spine, and legs (GALS) locomotor screen. Those with abnormal GALS screen were further interviewed and examined as per the American College of Rheumatology (ACR) *ad hoc* committee on clinical guidelines for the initial evaluation of adults with acute musculoskeletal symptoms.^[11]

Blood samples were drawn for ESR, viral loads and CD4+ T-lymphocyte cell count determination. HIV positivity was confirmed either by double ELISA (strip and micro-pit) or ELISA and Western blot. Patients with inflammatory arthritis additionally did serum uric acid, rheumatoid factor (RF) and antinuclear antibody tests (ANA). RF was done by latex agglutination test, and ANA tests were done by ELISA method. Standard digital radiographs of affected joints were taken in indicated subjects. Patients with hip and alternating buttock pains had plain radiography of both hips and sacroiliac joints (anteroposterior view) which were evaluated by same radiologist for features of avascular necrosis (AVN) and sacroiliitis, respectively. Synovial fluid was obtained, for analysis and microscopy, culture/sensitivity testing and acid fast *bacilli* detection in those with demonstrable joint effusion. The clinically evident articular features, laboratory, and radiographic findings were used to reach diagnosis of articular disorder. The diagnosis and classification for rheumatic articular disorders were based on ACR classification guidelines for these articular disorders^[4,12,13] but on European Spondyloarthropathy Study Group (ESSG) for spondyloarthropathy.^[14]

Statistical Package for Social Sciences 15 version (SPSS Inc., Chicago, IL, USA) was used for data entry, validation, and analysis.

Results

A total of 480 participants were recruited for the study comprising 240 HPS as test subjects and 240 HNS as control subjects. Both HPS and HNS were made up of 95 males and 145 females. The mean age of the HPS was 38.1 (10.2) years and ranged from 17 to 61 years. The controls had a mean age of 38.4 (10.5) years and ranged from 16 to 63 years. As expected, there was no statistically significant difference between the mean age of the HPS 38.1 (10.2) years and control 38.4 (10.5) years ($t = 0.305$, $P = 0.76$). Table 1a and b shows the age group distribution and the sociodemographics of the study population respectively.

Table 1a: Age group distribution of study population

Age group	Study population N (%)		Total N (%)
	Test	Control	
10-19	7 (2.9)	7 (2.9)	14 (2.9)
20-29	37 (15.4)	37 (15.4)	74 (15.4)
30-39	98 (40.8)	98 (40.8)	196 (40.8)
40-49	58 (24.2)	58 (24.2)	116 (24.2)
50-59	34 (14.2)	34 (14.2)	68 (14.2)
60-69	6 (2.5)	6 (2.5)	12 (2.5)
Total	240 (100.0)	240 (100.0)	480 (100.0)

Table 1b: The socio-demographic features of the study population

Variable	HIV+		HIV-	
	N	%	N	%
Occupational distribution				
Unemployed	15	6.3	9	3.8
Artisans	81	33.8	77	32.1
Student	16	6.7	23	9.6
Professional	36	15	33	13.6
Trader	67	27.8	71	29.6
Farmer	25	10.4	27	11.3
Marital status				
Single	177	73.8	158	65.8
Married	57	23.8	60	25.0
Divorced	6	2.5		
Co-habiting	0	0	11	4.6
Separated	0	0	10	4.2
Widow (er)	0	0	1	0.4

HIV: Human Immunodeficiency Virus

Occupational distribution and marital status of respondents

They are shown in Table 2. Across all articular disorder groups, artisans were the most frequently afflicted occupational group.

Viral load, CD4+ T-cell count and erythrocyte sedimentation rate of the study population

The mean viral load of the 240 HPS was 133,697.36 (315,732.5) copies/μl. The median viral load was 5488.5 copies/μl. The Mann–Whitney U-test showed that the ranked mean (146.5) of the viral load of HIV-positive HAART naïve subjects was significantly higher than that (94.50) of HIV-positive HAART exposed subjects (U = 4080.5, P = <0.01).

The mean CD4+ T-lymphocyte cell count of HPS and controls were respectively 326.57 (240.7) cells/μl and 951.35 (332.3)/μl, while the median CD4+ T-lymphocyte cell count of HPS and controls were 234.0/μl and 864.0/μl, respectively.

The mean ESR of HPS was 67.0 (42.4) mm 1st h while that of HNS was 15.0 (10.7) mm 1st h. There was statistically significant difference between the mean ESR of the HPS and HNS (t = 18.41, P < 0.01). Figure 1 shows the box plot

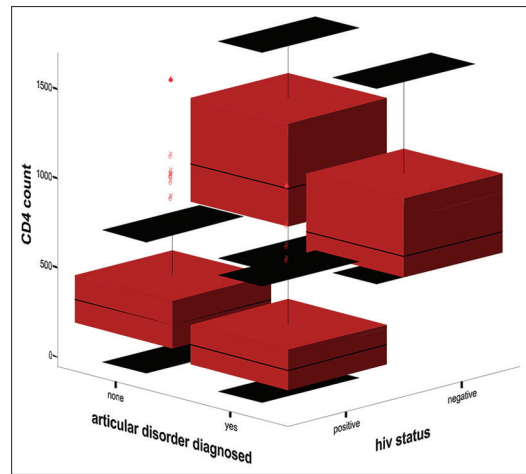


Figure 1: CD4+ T lymphocyte count, HIV status, and articular disorder of the study population

graph of CD4+ T-cell count, articular disorder, and HIV status of the study population. From the Figure 2, it is clear that the viral loads for both HPS with arthralgia and without arthralgia were similar while the CD4+ T-cell counts were higher for HPS without articular disorders than the HPS with articular disorders. Figure 2 shows viral load, Arthralgia, and CD4+ T-cell counts of HIV-infected subjects. Figure 3 shows box plot of ESR, articular disorder, and HIV status of the study population.

Highly active antiretroviral therapy and study population

One hundred and twenty of the 240 HPS (i.e., half) were on HAART.

Articular disorder diagnosis among HIV positive cases and controls

The frequency of all articular disorders in the population of HPS was 37.1% (89/240) while that among the control was 16.2% (39/240). There was statistically significant difference between the frequency of occurrence of articular disorders among the HPS and the controls ($\chi^2 = 26.63$ P = <0.01). The frequencies of the different articular disorders found among the HPS are as follows: Arthralgia (29.6%, 71/240), HIVAA (4.6%, 11/240), Reiter’s disease (1.3%, 3/240), undifferentiated spondyloarthropathy (1.3%, 3/240), and gout (0.4%, 1/240). Only arthralgia was found among HNS.

The characteristics of the subjects and that of the articular disorders (arthralgia and HIVAA) are shown in Tables 1-3.

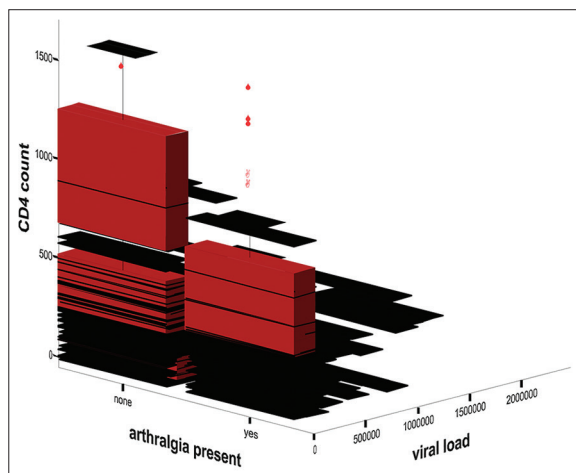
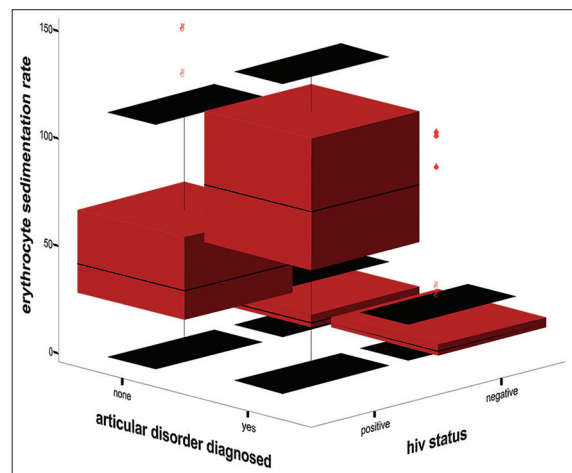
Predictors of arthralgia, HIV-associated arthritis, spondyloarthropathy and Reiter’s disease among HIV-positive subjects

The backward logistic regression analysis of the hypothesized factors that predict arthralgia among HPS was done. The ESR, duration of HAART, age, CD4+ T-cell count, and viral load of

Table 2a: The characteristics of HIV infected subjects with Arthralgia and HIV negative subjects with Arthralgia

Variable	HIV positive	N	Percent	HIV negative	N	Percent
Age group						
10-19		1	1.4		0	0
20-29		8	11.3		4	10.3
30-39		30	42.3		10	25.6
40-49		18	25.4		13	33.3
50-59		11	15.5		10	25.6
60-69		3	4.2		2	5.1
Marital status						
Single		56	78.9		23	59
Married		10	14.1		10	25.6
Divorced		5	7.0		0	0
Co-habiting		0	0		1	2.6
Separated		0	0		4	10.3
Widow(er)		0	0		1	2.6
Occupation						
Unemployed		2	2.8		0	0
Artisan		23	32.4		13	33.3
Student		2	2.8		2	5.1
Professional		16	22.5		6	15.4
Trader		16	22.5		7	17.9
Farmer		12	16.9		11	28.2
HAART status						
Naïve		36	50.7			
Exposed		35	49.3			
HAART regimens						
None		36	50.7			
Tenofovir, emtricitabine and Nevirapine		4	5.6			
Tenofovir, emtricitabine and Efavirenz		4	5.6			
Efavirenz, lamivudine and Abacavir		1	1.4			
Zidovudine, lamivudine and Nevirapine		26	36.			

HIV: Human Immunodeficiency Virus

**Figure 2:** Viral load CD4+ T-cell count and presence of arthralgia of the study population**Figure 3:** Erythrocyte sedimentation rate, presence of articular disorder and HIV status of study population

the HPS were entered. ESR and age were the best predictors of arthralgia presence (OR = 1.018, $P = <0.01$ for ESR) and (OR = 1.035, $P = 0.024$ for age). For every 2-fold increase in ESR, arthralgia is 101 times more likely to be present than absent. For every 3-fold increase in age, arthralgia is 103 times

more likely to be present than absent. Again looking at the contribution of each of the two variables with the other kept constant, 27.64% of the explained arthralgia variance was by ESR while only 5.25% by age. The overall specificity of this prediction was 71.7% that is quite good.

Table 2b: Characteristics of HIV positive subjects with Arthralgia

Variable	N	Percent
Complaint at HIV screening		
Others	51	71.8
Joint pain + others	17	23.9
Joint pain	2	2.8
Asymptomatic	1	1.4
Joint count		
Monoarticular	3	4.2
Oligoarticular	24	33.8
Polyarticular	44	62.0
Joint count		
Fingers	11	4.8
Shoulder	16	7.0
Hip	20	8.7
Wrist	28	12.2
Elbow	37	16.0
Knee	58	25.2
Ankle	60	26.1
Total	230	100.0
Pain severity		
Mild	29	40.8
Moderate	41	57.7
Severe	1	1
Functional status		
Class I	9	12.7
Class II	58	81.7
Class III	4	5.6
Class IV	0	0
WHO HIV disease stage		
State 1	1	1.4
State 2	60	84.5
State 3	10	14.1

HIV: Human Immunodeficiency Virus

The logistic regression analysis of hypothesized factors that predict HIVAA among HPS was done with CD4+ T-cell count, ESR, age, viral loads, and HIV disease duration entered into the equation initially. The result shows that only CD4+ T-cell count was predictive of HIVAA (OR = 0.994, $P = 0.01$). For every 6-fold decrease in CD4 T-cell count, HIVAA is 994 times more likely to be present than absent.

The logistic regression analysis of hypothesized factors that predict undifferentiated spondyloarthritis, Reiter's disease among HPS was done with CD4+ T-cell count, ESR, Age, viral loads, and HIV disease duration entered into the equation initially. The result shows that none was predictive of undifferentiated spondyloarthritis, Reiter's disease ($P > 0.05$ in all).

Discussion

Articular disorders are frequent but often under-diagnosed manifestation in patients infected with HIV.^[1-8] The prevalence of

Table 3: Characteristics of subjects with HIV Associated Arthritis

Variable	N	Percent
Age group		
30-39	6	54.5
40-49	4	36.4
60-69	1	9.1
Gender		
Male	8	72.7
Female	3	27.3
Occupation		
Artisan	4	36.4
Trader	4	36.4
Farmer	3	27.2
Presenting complaint at HIV screening test		
Arthritis	1	9.1
Others	7	63.6
Joint pain and others	3	27.3
HAART status		
Naïve	6	54.5
Exposed	5	45.5
Joint count classification		
Oligoarticular	8	72.7
Polyarticular	3	27.3
Pain severity		
Moderate	9	81.8
Severe	2	18.2
Functional status		
Class 2	7	63.6
Class 3	4	36.4
WHO HIV disease stage		
Stage 2	3	27.3
Stage 3	8	72.7

HIV: Human Immunodeficiency Virus

articular disorders in HPS has been reported to be 4.6–70%.^[4-8,10] The reported range is wide and reflects prevalence from different regions of the globe and can be explained by differences in definitions, in populations characteristics, and in environments. In Nigeria, Adelewo *et al.* reported five cases to illustrate the spectrum of rheumatological manifestations of HIV among Nigerians.^[15] In other parts of Africa and globally, available reports are on the rate of positivity to HIV antibodies among patients with certain articular disorders.^[16,17] This study has added further statistics to the available studies and case reports on articular disorders among HIV-infected persons.^[5,6,8,10,13-18] The prevalence of articular disorders in HPS of 37.1% found in this study is in keeping with previous reports of 4.6–70%.^[2,4-8,10,13] The significantly higher prevalence compared to controls suggested that HIV infection may be associated with articular disorders. The prevalence got in this study may be close to the true value because the subjects recruited for this prospective study were evaluated and classified based on ESSG and ACR classification guidelines for these articular disorders. Again viral infection like hepatitis viruses C and B were excluded during recruitment of subjects.

The similarity of the overall occupational distributions of the HPS and controls reflect the occupational distribution of residents of Enugu. Across all articular disorder groups, Artisans were the most frequently afflicted occupational group. This is worrisome because being artisans they needed their joints to be functionally optional. The increased joint problem among these artisans with HIV infection predisposes them to functional impairment and decreased productivity thereby deepening the burden that HIV infections had put on them.

The articular disorder types among HIV-positive and HIV-negative subjects

The articular disorders reported among HPS include Reiter's syndrome, HIV-associated arthritis, painful articular syndrome, acute symmetric polyarthritis, undifferentiated spondyloarthropathy, AVN of bone heads, septic arthritis, arthralgia, psoriatic arthritis, and gout. The control population also have articular disorders reportedly including any form of articular disorder including inflammatory, infective, degenerative, and neoplastic articular disorders.

The design of this study excluded the articular disorders that are degenerative, neoplastic or related to medications other than HAART. Thus persons with osteoarthritis, tuberculostatic medications, medications with hyperuricemia adverse effects, malignancies were not recruited as subjects.

The HPS in this study was found to have only arthralgia, HIV-associated arthritis, Reiter's disease, gout and undifferentiated spondyloarthropathy. None had painful articular syndrome, acute symmetric polyarthritis, AVN of head of bone, septic arthritis, and psoriatic arthritis.

The absence of painful articular syndrome and acute symmetric polyarthritis may be explained by the fact that their prevalence was very low among the HPS in Enugu to be picked in the course of the cross-sectional study or that the HPS in the recruitment area Enugu do not have these articular disorder types. Their being acute and transient articular disorders may have made their prevalence to be very low and thus not found within the study population and period.

The absence of AVN of head bone and psoriatic arthritis may be a characteristic of HPS in the areas of recruitment. For the AVN, the recruited subjects had HIV infection, half were on HAART but median/mean CD4+ T-cell count were well above 60/ μ l. The HIV positivity and percentage of them on HAART were among the reported risk factors for AVN.^[19] But CD4+ T-cell count less 60/ μ l was reported as a risk factor for development of AVN of head of bone.^[19]

The absence of septic arthritis is interesting. Septic arthritis was thought to be expectedly high among HPS. However, overtime this has proved to be untrue. There has not been demonstration of any clear relationship between CD4 count and septic

arthritis.^[20] In fact, HIV predisposing to septic arthritis has been disputed.^[20] It is rather increasingly thought to be related to simultaneous intravenous drug abuse. This era of increased HIV awareness, better health seeking behavior of HIV-infected subjects, early diagnosis, HAART and availability of more potent antibiotics may be the explanation for the absence of septic arthritis among the HPS studied. Moreover, intravenous drug abuse is not common in Enugu Nigeria.

For the HNS, the articular disorder found among them was arthralgia. Exclusion criteria eliminated most of the other articular disorders (osteoarthritis, malignant arthropathies, trauma, etc.) that could be seen among the subjects.

Predictors of articular disorders among HIV subjects

The ESR and age of HPS were both found to be predictive of Arthralgia. Every 2-fold increase in ESR value was predictive of 101 times likelihood of arthralgia presence than arthralgia absence while increase 3-fold in age was required for 103 likelihood of arthralgia presence than absence suggesting that ESR of the subjects was a better predictor of arthralgia presence than age. ESR is a marker of systemic inflammation, hence higher ESR values, indicating widespread systemic inflammation may explain the significantly higher frequency of arthralgia with higher ESR values. It also explains partly the predictability of arthralgia incidence with higher ESR. For the age, older age goes with same immune dysregulation which is worse in the HIV-infected persons. The contribution of age to prediction as shown in the result is small; however the immune dysregulation and the wear and tear that goes with aging may be the explanation for increasing frequency/predictability of arthralgia with advancing age.

The logistic regression strongly suggested that ESR, age, viral loads, and CD4+ T-lymphocyte count have no relationship with Reiter's disease and undifferentiated spondyloarthropathy among the HPS studied. Reiter's disease has been reported in HIV disease among young sexually active persons. It is thought to be strongly linked to the sexually transmitted disease presence in the HIV-infected persons. It is an autoimmune inflammatory process directed against the joint elements mimicking components of infective sexually transmitted agents. Thus age, viral loads, CD4+ T-lymphocyte count may not be predictive of Reiter's syndrome and undifferentiated spondyloarthropathy as seen in this study.

Logistic regression analysis was done for the HIV patients with HIVAA. Of the five continuous variables (VL, CD4+ T-lymphocyte count, age, ESR, HIV disease duration) entered initially, only CD4+ T-lymphocyte count was found to be predictive of HIV-associated arthritis.

Strengths and limitations

We could not do all possible tests to exclude possible confounding etiologies of articular disorders. So there was still

a possibility of misclassifications. There is also a possibility that our HIV patients presented with asymptomatic exclusion criteria (e.g., HIV with malignancy) then causing confusion. However, because we matched our test subjects and controls, drew the two samples also from same recruitment area, in same geographical and had same exclusions and inclusions criteria for both sub-populations, there is no reason why this possibility of misclassification would affect our results.

Conclusion

The study showed that articular disorders are commoner among HPS than HNS. HIV infection may have a significant effect on articular disorder development. Arthralgia was the most frequent articular disorder among both HPS and HNS. ESR and age were the best predictors of Arthralgia presence among HIV-infected patients. CD4+ T-cell count was predictive of HIV-associated arthritis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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