Entheseal involvement in asymptomatic human immunodeficiency virus infected patients: preliminary results of a clinical and ultrasonographic study

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Abstract

Objective

As a strong association between human immunodeficiency virus (HIV) infection and spondyloarthritis (SpA) has been hypothesised, our main objective was to explore by power Doppler ultrasonography (PDUS) the presence of subclinical enthesitis in asymptomatic HIV patients. The presence of subclinical synovitis was also evaluated.

Methods

Consecutive asymptomatic HIV patients were studied and compared with asymptomatic HCV patients and healthy controls (HC). All subjects underwent a clinical and PDUS bilateral examination of the following entheses and joints: epicondyle, quadriceps, patellar, Achilles and plantar fascia; wrists, II and III metacarpo-phalangeal, knee and ankle.

Results

Twenty-nine HIV, 32 HCV and 25 HC were recruited; 1.032 entheses and 860 joints were examined. Clinical diagnosis of enthesitis was made in 10.3% HIV patients, 6.2% HCV patients (p=0.66) and none HC (p=0.24). PDUS enthesitis was found in 72.4% HIV, 28.1% HCV (p=0.0008) and 12% HC (p<0.0001). Clinical diagnosis of synovitis was made in 3.4% HIV patients, 9.3% HCV patients (p=0.61) and none HC (p=1). PDUS abnormalities were documented in 24.1% HIV patients, 71.8% HCV patients (p=0.0003) and none HC (p=0.0001). In detecting enthesitis and synovitis, PDUS was more sensitive than clinical examination both in HIV and HCV patients.

Conclusion

Our preliminary study shows the high frequency of PDUS enthesitis in asymptomatic HIV patients, which highlights the close link between HIV and SpA. Further studies are desirable on a larger number of HIV patients to confirm these results. PDUS proved to be more sensitive than clinical examination in detecting subclinical involvement of entheses and joints.

Key words

HIV, HCV, enthesitis, synovitis, ultrasonography, power Doppler, spondyloarthritis

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Introduction

Rheumatic manifestations are one of the most common features associated with human immunodeficiency virus (HIV) infection (1-3). They can occur at any stage of the disease and include articular and extra-articular rheumatologic syndromes. The latter encompass a number of conditions such as osteonecrosis, polymyositis, vasculitides and pyomyositis (4-9). Articular syndromes include HIV-associated arthropathy (HAA) and painful articular syndrome (PAS), both considered specifically related to HIV infection (1, 10-13). Furthermore, definite articular conditions belonging to the wide spectrum of spondyloarthritis (SpA) such as reactive arthritis (ReA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) and undifferentiated SpA (uSpA) have also been frequently reported in association with HIV infection, which led to suggest a strong association between HIV and SpA (2, 10, 14, 15).

Enthesitis is a distinctive and frequently under-diagnosed feature of SpA (16, 17). Ultrasonography (US) with power Doppler (PD) has proved to be a highly sensitive imaging method in detecting both structural and vascular entheseal changes and is now universally deemed essential for the diagnosis of enthesitis either in the presence or absence of clinical symptoms (16, 18).

The main aim of our study was to explore by US the presence of subclinical enthesitis in a cohort of consecutive HIV patients without rheumatic symptoms in comparison with healthy subjects and a group of asymptomatic HCV patients. Secondary objectives were to evaluate by PDUS the prevalence of subclinical synovitis, and to compare clinical examination with PDUS in detecting entheseal and joint abnormalities.

Materials and methods

From June 2014 to November 2016, all consecutive recently diagnosed (<12 months) HIV patients attending the local Infectious Disease Department were referred to the Rheumatology Unit of the University of Ferrara (Italy) to be studied. As controls, patients with HCV infection (disease duration: 9–23 months) and a group of healthy subjects matched for sex and age and without any markers of HIV or HCV infection were recruited. To be enrolled in the study, all HIV and HCV patients should not be suffering from pain at joints, entheses or spine and should not take any antiviral treatment. Exclusion criteria were major trauma, metabolic and degenerative diseases, surgical interventions on joints, corticosteroids injection within the previous 6 months, the practice of agonistic sports, history of cancers, acute infections or hepatitis B surface antigen. All patients should not be HCV and HIV co-infected.

HIV infection was diagnosed by the demonstration in the serum of antibodies to HIV obtained by chemiluminescence immunoassay (CLIA) (Diasorin) and successively confirmed by Western Blot. HIV- RNA detection by polymerase chain reaction (RT-PCR Real time, Roche) and CD4/CD8$^+$ cell count were performed in all patients. According to CDC Classification System for HIV-Infected Adults and Adolescents (19), 27 HIV patients (93.1%) were stage A, 1 (3.4%) stage B1 and 1 (3.4%) stage C2. Chronic C hepatitis was diagnosed by the demonstration in the serum of antibodies to HCV obtained by CLIA (Diasorin) and successively confirmed by the more specific line immunoassay (LIA, Fujirebio). HCV-RNA detection by PCR (RT-PCR Real time, Roche) and HCV genome (Line Probe Assay, Siemens) were performed in all patients. Other serological tests were performed in HIV and HCV patients if clinically indicated or as part of the usual routine follow-up assessment (*i.e.* blood cell count, kidney function, liver function tests, urinalysis and, in HCV patients, anti-mitochondrial antibodies (AMA), anti-smooth muscle antibodies (ASMA), anti-liver- kidney antibodies (LKM), anti-thyroid peroxidase antibodies (anti-TPO) and cryoglobulinaemia. Detection of antinuclear antibodies, rheumatoid factor and evaluation of inflammation parameters (C-reactive protein, ESR) were not included in the protocol. Written informed consent was obtained from all the participants and the study has been approved by the institutional independent ethical committee of the "Azienda Ospedaliera-Universitaria

S. Anna di Ferrara". The study was conducted according to the principles of the Declaration of Helsinki.

All subjects underwent a clinical and US examination of the following bilateral entheses and joints: common extensor tendon insertion on the lateral humeral epicondyle (CET); quadriceps tendon insertion at the superior pole of patella (QT); patellar tendon (PT) insertion at the inferior pole of the patella (proximal PT: pPT) and at the tibial tuberosity (distal PT: dPT); Achilles tendon (AT) and plantar fascia (PF) insertion on the calcaneus; radiocarpal joints (RCj), II and III metacarpo-phalangeal (MCP) joints, knee and ankle joints. Clinical and US examination were performed separately by two blinded rheumatologists.

Clinical assessment

Clinical examination of entheses and joints was performed before US examination by a qualified rheumatologist (FF) who was blinded of US evaluation. Enthesitis was defined by the presence of at least one of the following findings: spontaneous pain; tenderness elicited by pressure; and local swelling (20). Synovitis was defined by the presence of pain and swelling at the examined joints. All subjects were evaluated using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (21), Bath Ankylosing Spondylitis Functional Index (BASFI) (22) , Health Assessment Questionnaire (HAQ) (23) and patient's visual analogue scale (VAS) on global disease activity (0–100 mm).

PDUS assessment

US examination was performed by a rheumatologist experienced in musculoskeletal sonography (G.C.) who was unaware of the subjects clinical data. An APLIO XG machine (Toshiba Medical System Corporation) equipped with a multifrequency linear array transducer, range 7–18 MHz, was used. The sonographer was unaware of clinical examination and of HIV or HCV diagnosis. Settings for PD were: scale 3.8 cm/sec; pulse repetition frequency: 23.4 KHz for entheses, wrists, MCP and 13.9 KHz for knee and ankle; and low filters. Colour gain was adjusted just below the level that caused the appearance of noise artefacts (40–50 dB). The temperature of the room was set to 20°C (20).

All patients and controls underwent a longitudinal and transverse US examination of the explored entheses and joints in grey-scale modality, to detect morphologic abnormalities and subsequently with PD to detect abnormal vascularisation (20, 24).

According to Terslev *et al*., the following abnormal alterations were considered as PDUS signs of enthesitis: hypoechogenicity, increased thickness, enthesophytes, calcifications, erosions at bone insertion and Doppler activity (25). Grey-scale US alterations were recorded as absent or present, and increased thickness of entheses was evaluated as follows: QT>6.1 mm; pPT and dPT >4 mm; AT >5.29 mm; PF >4.4 mm; CET >4.6 mm (26, 27). Doppler activity was studied approximately <2 mm near the bony cortex, scored as a binary item (negative/positive) and semi-quantitatively graded [no flow (Grade 0); mild (only one spot) (Grade 1); moderate (two spots) (Grade 2); severe (more than three spots) (Grade 3)] (25, 28). The presence of bursitis (a well circumscribed, localised anechoic or hypoechoic area at the site of an anatomical bursa, compressible by the transducer, and >2 mm in the short axis) (20, 26) was also recorded at each site.

According to D'Agostino *et al*. (20), each US enthesitis was classified into 5 distinctive patterns: Stage 1: Vascularisation at the cortical junction without abnormal findings in B mode; Stage 2a: vascularisation associated with swelling and/or decreased echogenicity at the cortical junction in B mode; Stage 3a: same as stage 2a, plus erosions of cortical bone and/or calcification of enthesis, and optional surrounding bursitis; Stage 2b: abnormal findings in B mode as in stage 2a, but without vascularisation; and Stage 3b: abnormal findings in B mode as in stage 3a, but without vascularisation. A total PD score by summing semi-quantitative PD scores of each enthesis (tPD) was also calculated (29).

The US assessment of the joints included evaluation of RCj, II and III MCP joints (dorsal side), suprapatellar recesses of the knee and tibio-talar joint. In each joint was evaluated the presence of synovial fluid (SF), synovial hypertrophy (SH), and intra-articular PD signal, registered according to the OMERACT definitions (30). SF, SH and PD were evaluated as present or absent and also graded in a 0-3 semi-quantitative score [SF and SH: 0=absent, 1=mild, 2=moderate, 3=marked; PD: 0=absent, 1=mild (≤3 PD signals), 2=moderate (≥3 PD signals in <50% of synovial area) and 3=marked (≥3 PD signals in >50% of synovial area)] (24, 30).

Based on the presence/absence of SF, SH and PD, three US scenarios were considered: normal aspect (SF- and SH-/PD-); active synovitis (SF+ and/or SH+/PD+); inactive synovitis (SF+ and/or SH+/PD-) (31). A total score by summing the scores obtained from each joint was also separately calculated for SH (tSH), SF (tSF) and PD (tPD).

US inter-and intra-observer agreement was estimated by recording in a digital archiving computer system the images of all patients and HC. All saved images were read three months after the initial scanning by the same rheumatologist who performed US examination (GC) and by another rheumatologist expert in musculoskeletal US (IF) both blind to previous results. The identity of patients was mixed with controls.

Statistical analysis

Differences between groups were examined using two-tailed Fisher's exact test by GraphPad software. A p-value <0.05 was assumed as statistically significant. Inter- and intraobserver agreement for US examination were calculated using an unweighted k test. A k value <0.40 was considered low; 0.41–0.60: moderate; 0.61–0.80 good; 0.81–1 excellent.

Results

29 HIV patients [male/female ratio 23/6, mean age ± SD: 44±8.7 years, mean BMI: 24±3, Caucasian race, mean HIV viral load ± SD: 47.231±43.401 copies/ml, mean CD4 count± SD: 631±289 cells/mm^3], 32 HCV patients [male/female ratio 19/13, mean age± SD: 48.5±12.7, mean BMI: 28±3.1,

mean HCV viral load ± SD: 3.03±2.59 x10^6 UI/ml] and 25 healthy controls (HC) [male/female ratio 22/3, mean age± SD: 47±8.1, BMI: 27,1±3] were studied. A total number of 1.032 entheses (348 in HIV, 384 in HCV and 300 in HC) and 860 joints (290 in HIV, 320 in HCV and 250 in HC) were examined. In both HIV and HCV patients no significant alterations of routine haematological tests were appreciable. AMA and cryoglobulins were negative in all HCV patients. ASMA, LKM and anti-TPO were positive in 3, 1 and 2 HCV patients, respectively. 1b genotype was present in 65.6% HCV patients, 2a in 21.8%, 1a in 6.2 % and 3a in 6.2%. In both HIV and HCV groups, no correlations between available laboratory data with PDUS changes were found that would help to distinguish patients with entheses or joints alterations and patients without. All patients and controls answered negatively to BASFI, BASDAI, HAQs and pain VAS (0–100).

Enthesitis

On clinical examination, a diagnosis of enthesitis was made in 3 HIV patients (10.3%), 2 HCV patients (6.2%) (p=0.66) and none HC (p=0.24). Of all the examined entheses, were considered clinically abnormal 4 HIV entheses (1.1%), 3 HCV entheses (0.7%) (p=0.71) and none HC entheses (p=0.12) (Table I).

On PDUS examination, at least one abnormality was found in 21 HIV patients (72.4%), 9 HCV patients (28.1%) (p=0.0008) and 3 HC (12%) (p<0.0001). Of all the examined entheses, were considered abnormal (at least one abnormality) 113 HIV (32.4%), 25 HCV (6.5%) (p<0.0001) and 10 HC (3.3%) (p<0.0001) entheses (Table I).

Among the PDUS altered entheses, no significant differences emerged between HIV and HCV patients with regard to the involvement of single entheses (Table II) and the individual detected alterations, with the only exception of power Doppler that was significantly abnormal in HIV (22.1%) compared to HCV (4%) altered entheses (p=0.04) (Table III). Coherently, considering the maximum achievable PD score (*i.e.* 339 in the 113 HIV, and 75 in the 25 HCV altered entheses), tPD was higher in HIV than in HCV (42 *vs.* 1). In HIV, there was no significant difference between the frequency of single-altered entheses in lower limbs in comparison with that found in upper limbs (CET) (Table II).

By comparing HCV and HC, the prevalence of PDUS enthesitis was not significantly different between the two groups [28.1% HCV patients *vs.* 12% HC (p=0.19); 6.5% of HCV *vs.* 3.3% of HC examined entheses (p=0.07)] (Table I).

PDUS was significantly more sensitive than clinical examination in detecting enthesitis both in HIV (32.4% *vs.* 1.1%; p<0.0001) and HCV (6.5% *vs.* 0.7%; p<0.0001) patients.

Classification of the altered entheses by combining grey-scale and PD features is reported in Table IV. Individual PDUS abnormalities that were not classifiable (*i.e.* isolated thickness) are reported separately. Abnormalities with vascularisation (1+2a+3a) were significantly more frequent in HIV (22.1%) than in HCV (4%) (p=0.04). There were no significant differences between the two groups regarding the abnormality without vascularisation (2b+3b) (69% and 64%, respectively) (p=0.64).

Synovitis

On clinical examination, a diagnosis of synovitis was made in 1 HIV patients (3.4%), 3 HCV patients (9.3%) (p=0.61) and none healthy control (p=1). Of all the examined joints, were considered clinically abnormal 2 HIV joints (0.6%), 5 HCV joints (1.5%) (p=0.45) and none HC joint (p=0.5) (Table V).

Table I. Clinical and US evidence of enthesitis in HIV, HCV and HC.

	HIV	HCV	HC
Subjects, n	29	32	25
Clinical enthesitis, n (%)	3 (10,3)	2 (6.2) p=0.66	0 p=0.24
		p=0.49	
PDUS alterations (at least one) n (%)	21 (72,4)	9 (28.1) p=0.0008	3 (12) p<0.0001
		p=0.19	
Total entheses examined, n.	348	384	300
Clinical enthesitis, n (%)	4 (1.1)	3 (0.7) p=0.71	0 p=0.12
		p=0.26	
PDUS alterations (at least one), n (%)	113 (32.4)	25 (6.5) p<0.0001	10 (3.3) p<0.0001
		p=0.07	

HIV: human immunodeficiency virus; HCV: Hepatitis C virus; HC: healthy controls; PDUS: power Doppler ultrasonography.

Table II. Frequency of PDUS involvement of each enthesis in HIV and HCV.

	HIV n=113	HCV n=25	HC n=10
CET, n (%)	15 (13.2)	5 (20) p=0.35	2 (20) p=0.5
QT, n (%)	15 (13.2)	3 (12) p=1	1 (10) p=0.7
pPT, n (%)	14 (12.3)	0 p=0.07	1 (10) p=0.8
dPT, n (%)	24 (21.2)	8 (32) p=0.29	2 (20) p=1
AT, n (%)	22 (19.4)	6 (24) p=0.59	2 (20) p=1
PF, n (%)	23 (20.3)	3 (12) p=0.4	2 (20) p=1

HIV: human immunodeficiency virus; HCV: Hepatitis C virus; HC: healthy controls; CET: common extensor tendon; QT: quadriceps tendon; pPT: proximal patellar tendon; dPT: distal patellar tendon; AT: Achilles tendon; PF: plantar fascia.

Table III. PDUS abnormalities in the altered HIV and HCV enthuses.

	CET		QT		pPT		dPT		AT		PF		All sites		
	HIV n=113	HCV n=25	HIV n=113	HCV n=25	HIV n=113	HCV n=25	HIV n=113	HCV n=25	HIV n=113	HCV n=25	HIV n=113	HCV n=25	HIV n=113	HCV n=25	*p*
Thick, n (%)	10 (8.8)	3 (12)	13 (11.5)	2 (8)	9 (7.9)	-	15 (13.2)	2 (8)	16 (14.1)	3 (12)	17 (15)	2 (8)	80 (70.7)	12 (48)	0.09
Hypo, n (%)	11 (9.7)	2 (8)	9 (7.9)	2 (8)	12 (10.6)	-	13 (11.5)	3 (12)	17 (15)	2 (8)	11 (9.7)	3 (12)	73 (64.6)	12 (48)	0.17
Ent, n (%)	4 (3.5)	1 (4)	5 (4.4)	1 (4)	5 (4.4)	-	6 (5.3)	3 (12)	8 (7)	2 (8)	7 (6.1)	2 (8)	35 (30.9)	9 (36)	0.64
Calc, n (%)	2 (1.7)	2 (8)	3 (2.6)	-	2 (1.7)	-	4 (3.5)	3 (12)	4 (3.5)	1 (4)	5 (4.4)	-	20 (17.6)	6 (24)	0.57
Er, n (%)	1 (0.8)	-	-	-	-	-	1 (0.8)	1 (4)	6 (5.3)	1 (4)	1 (0.8)	-	9 (7.9)	2 (8)	1
Burs, n (%)	-	-	1 (0.8)	-	1 (0.8)	-	12 (10,6)	3 (12)	5 (4.4)	1 (4)	-	-	19 (16.8)	4 (16)	1
a-PD , n (%)	6 (5.3)	-	1 (0.8)	-	1 (0.8)	-	3 (2.6)	-	8 (7)	1 (4)	6 (5.3)	-	25 (22.1)	1 (4)	0.04
PD max score													339	75	
tPD	7	0	2	0	1	0	6	0	16	1	10	0	42	1	

HIV: human immunodeficiency virus; HCV: Hepatitis C virus; CET: common extensor tendon; QT: quadriceps tendon; pPT: proximal patellar tendon; dPT: distal patellar tendon; AT: Achilles Tendon; PF: plantar fascia; Thick: thickness; Hypo: hypoechogenicity; Ent: enthesophytes; Calc: bone junction calcific deposits; Er: erosions; Burs: bursitis; a-PD: altered PD at bony insertion; tPD: total power Doppler.

Table IV. Classification of HIV and HCV altered entheses by combining grey-scale and PD features.

	Stage 1, n		Stage 2a, n		Stage 3a, n		1+2a+3a, n		Stage 2b, n		Stage 3b, n		2b+3b, n		Isolate thick, n		Isolate hypo, n		Isolate Ent/ Calc, n		Isolate burs, n		Total altered entheses, n	
	HIV	HCV	HIV	HCV	HIV	HCV	HIV	HCV	HIV	HCV	HIV	HCV	HIV	HCV	HIV	HCV	HIV	HCV	HIV	HCV	HIV	HCV	HIV	HCV
CET, n	2	-	1	-	3	-	6	-	5	3	3	-	8	3	1	1	-	-	-	1	-	-	15	5
QT, n	-	-	-	-	1	-	1	-	4	1	8	-	12	1		-	-	1	-	1	1	-	15	3
pPT, n	-	-	-	-	1	-	1	-	4	-	6	-	10	-	1	-	1	-	1	-	-	-	14	-
dPT, n	1	-	2	-	-	-	3	-	6	4	11	2	17	6	-	-	-	-	-	-	4	2	24	8
AT, n	1	-	2	1	5	-	8	1	3	3	11	1	14	4	-	-	-	-	-	-	-	1	22	6
PF, n	1	-	4	-	1	-	6	-	6	2	11	-	17	2	-	1	-	-		-	-	-	23	3
Total n (%)							25 (22.1)	1 (4)					78 (69)	16 (64)	3 (2.6)	2 (8)	1 (0.8)	1 (4)	1 (0.8)	2 (8)	5 (4.4)	3 (12)	113	25
							p=0.04						*p*=0.64											

HIV: human immunodeficiency virus; HCV: Hepatitis C virus; CET: common extensor tendon; QT: quadriceps tendon; pPT: proximal patellar tendon; dPT: distal patellar tendon; AT: Achilles tendon; PF: plantar fascia; Thick: thickness; Hypo: hypoechogenicity; Ent/Calc: enthesophyte and/or bone junction calcific deposits; Burs: bursitis

On PDUS examination, synovitis was documented in 7 HIV patients (24.1%), 23 HCV patients (71.8%) (p=0.0003) and none HC (p=0.0001). Of all the examined joints, were considered abnormal (at least one abnormality) 19 HIV joints (6.5%), 82 HCV joints (25.6%) (p<0.0001) and none HC joint (p<0.0001) (Table V).

In detecting synovitis, PDUS was significantly more sensitive than clinical examination both in HCV (25.6% *vs*. 1.5%; p<0.0001) and HIV (6.5% *vs*. 0.6%; p=0.0002) patients. By comparing HCV and HC, the prevalence of PDUS synovitis was significantly higher in HCV (71.8% patients; 25.6% of all examined joints) than in HC [none subject (p<0.0001); none joint (p<0.0001)] (Table V).

Although not statistically significant, HIV joints of lower limbs (knee and ankle) (63.1%) were more frequently involved than those of upper limbs (RCj, II and III MCP) (36.8%) (p=0.19). In HCV patients, joints of upper limbs (59.7%) were significantly more involved than lower limbs (42.6%) (p=0.04) (Table VI).

PDUS abnormalities detected in HIV and HCV altered joints are detailed in Table VII.

Considering all the altered joints and the maximum achievable score for each of the three parameters SF, SH and PD (57 in the 19 HIV and 246 in the 82 HCV altered joints), tSF, tSH and tPD were higher in HCV (112, 32 and 42) than in HIV (24, 2 and 2, respectively). Classification of the altered joints based on the presence/absence of SF, SH and PD is reported in Table VIII. Active synovitis (SH and/or SF+/PD+) was significantly higher in HCV (40.2%) than in HIV patients (10.5%) (p=0.01), while inactive synovitis (SH and/or SF+/ PD-) was significantly higher in HIV (89.4%) than in HCV patients (59.7%)(p=0.01).

There was an excellent level of intra- (κ=0.96) and inter- (κ=0.87) observer agreement for the PDUS evidence of enthesitis and synovitis.

Discussion

A complex variety of rheumatological conditions can occur in the course of HIV infection, often representing the initial presentation of the disease (4-9). HAA and PAS are the most typical articular syndromes, both considered specifically related to HIV infection (1, 10-13). Moreover, definite diseases belonging to the wide spectrum of SpA such as ReA, PsA, AS and uSpA have also been frequently reported during HIV infection, so a strong association between HIV and SpA and a possible pathogenic role for HIV in SpA have been

hypothesised (2, 10, 14, 15). On this ground, our US study was undertaken to explore in HIV patients without musculoskeletal symptoms the presence of subclinical enthesitis, which represent a distinctive feature of SpA (16, 17). To the best of our knowledge this is the first ultrasonographic study aimed at detecting the presence of entheses and joint alterations in HIV patients without articular symptoms. Entheses have a relevant role in the pathogenesis of SpA (32) and peripheral enthesitis are included in the Amor (33), ESSG (34) and Assessment in Spondylo Arthritis International Society for axial SpA (ASAS) (35) classification criteria. PDUS has proved to be highly sensitive in detecting both structural and vascular alterations either in the presence or absence of clinical symptoms (16, 17, 20, 26). The significant higher frequency of PDUS enthesitis that we have found in HIV patients compared to both HCV patients and HC, as well as the significantly greater rate of enthesitis than synovitis within the group of patients with HIV highlight the close link between HIV and SpA. This relationship appears to be further supported by other observations. First, HAA and PAS show clinical features similar to those observed in SpA (36). HAA usually occurs as an asymmetric oligoarthritis that predominantly involves the lower extremities (knees and ankles), has a male preponderance, tends to be short-lived with a peak intensity occurring in 1 to 6 weeks but in some cases may have a chronic course with erosions, joint destruction and in some cases radiological signs of new bone formation (11-13, 37). PAS, reported in 5–13% of cases, is characterised by severe arthralgias with few objective findings and usually self-limiting course in 24–48 h, but sometimes more persistent and susceptible of progressing to inflammatory joint diseases. Lower extremities are the most involved in an asymmetric pattern, pain is severe and patients experience marked funcional disability (1, 10, 11, 38).

Secondly, the spectrum of rheumatic conditions associated with HIV has substantially changed after the introduction of highly active antiretroviral therapy (HAART). Indeed, the incidence of PAS and HAA as well as ReA and PsA, which dominated epidemiological studies in the pre-HAART era, has dramatically decreased in the post-HAART era, while new disorders including osteonecrosis, osteoporosis, osteomyelitis and the immune reconstitution inflammatory syndrome (IRIS) have become prevalent (10, 39).

All these data allow to hypothesise that entheses could be a key musculoskeletal target in the course of HIV infection, and that PAS and HAA could actually belong to the broad group of Spondyloenteso-arthritis. A PDUS study of entheses and joints in symptomatic HIV patients with PAS and HAA could help to clarify this issue.

Because of the heterogeneity of musculoskeletal symptoms observed in HIV infection, screening for HIV in rheumatic disease has been suggested by several authors, especially in patients with

Table V. Clinical and US evidence of synovitis in HIV, HCV and HC.

	HIV	HCV	HC
Subjects, n	29	32	25
Clinical synovitis, n (%)	1 (3.4)	3 (9.3) p=0.61	0 p=1
		p=0.24	
PDUS alterations (at least one), n (%)	7 (24.1)	23 (71.8) p=0.0003	0 p=0.0001
		p<0.0001	
Total joints examined, n	290	320	250
Clinical synovitis, n (%)	2 (0.6)	5 (1.5) p=0.45	0 p=0.5
		p=0.07	
PDUS alterations (at least one), n (%)	19 (6.5)	82 (25.6) p<0.0001	0 p<0.0001
		p<0.0001	

HIV: human immunodeficiency virus; HCV: Hepatitis C virus; HC: healthy controls; PDUS: power Doppler ultrasonography.

Table VI. Frequency of PDUS joints involvement in HIV and HCV.

	HIV n=19	HCV n=82
RCj, n (%)	3 (15.7)	33 (40.2) p=0.06
II MCP, n (%)	2 (10.5)	7 (8.5) p=0.67
III MCP, n (%)	2 (10.5)	9 (10.9) p=1
Total upper limbs, n (%)	7 (36.8)	49 (59.7) p=0.07
Knee, n (%)	8 (42.1)	19 (23.1) p=0.14
Ankle, n (%)	4 (21)	16 (19.5) p=1
Total lower limbs, n (%)	12 (63.1)	35 (42.6) p=0.12

HIV: human immunodeficiency virus; HCV: Hepatitis C virus; RCj: radiocarpal joint; MCP: metacarpophalangeal.

Table VII. PDUS abnormalities detected in HIV and HCV altered joints.

	RDj		II MCF		III MCF		Knee		Ankle		All sites		*p*
	HIV n=19	HCV n=82	HIV n=19	HCV n=82	HIV n=19	HCV n=82	HIV n=19	HCV n=82	HIV n=19	HCV n=82	HIV n=19	HCV n=82	
SF, n (%)	3 (15.7)	31 (37.8)	2 (10.5)	7 (8.5)	2 (10.5)	9 (10.9)	8 (42.1)	19 (23.1)	4 (21)	16 (19.5)	19 (100)	82 (100)	1
SH, n (%)	-	10 (12.1)	-	-	-	-	2 (10.5)	7	-	3 (15.7)	2 (10.5)	20 (24.3)	0.23
a-PD, n (%)	-	11 (13.4)	-	3 (15.7)	-	4 (4.8)	2 (10.5)	10 (12.1)	-	5 (6)	2 (10.5)	32 (39)	0.02
SH,SF,PD max score											57	246	
tSF	5	49	2	9	2	10	10	26	5	18	24	112	
tSH	-	18	-	-	-	-	2	11	-	3	2	32	
tPD	-	15	-	3	-	4	2	14	-	6	2	42	

HIV: human immunodeficiency virus; HCV: Hepatitis C virus; RCj: Radiocarpal joint; MCP: metacarpophalangeal; SF: synovial fluid; SH: synovial hypertrophy; a-PD: altered power Doppler; tSH: total score synovial hypertrophy; tSF: total score synovial fluid; tPD: total score power Doppler.

established diseases such as rheumatoid arthritis or systemic lupus erythematosus who present new atypical musculoskeletal symptoms while receiving immunosuppressive therapy (40, 41). Our results are in keeping with this recommendation, and suggest a particular attention to patients with aspecific multifocal rheumatologic symptoms resembling SpA or in definite SpA under pharmacological treatment where new musculoskeletal symptoms do appear.

Among the altered HIV entheses, the prevalence of enthesitis with vascularisation was lower than enthesitis without vascularisation. This result appears consistent with the fact that all patients were asymptomatic. However, this prevalence was significantly lower than that reported by D'Agostino *et al*. in SpA (81%) (20), but higher than that reported in SpA by Spadaro *et al*. (6%) (42). It would be rather interesting to carry out a comparative study between SpA and HIV patients to verify the real prevalence of subclinical active enthesitis in the two groups.

In keeping with the available literature data (20, 26, 43), in our work PDUS proved to be more sensitive than clinical examination in detecting subclinical involvement of entheses and bursae. However, unlike other studies (20, 26), no discrepancy between clinical and PDUS evaluation emerged and PDUS examination confirmed the physical examination in all cases, as shown in our previous study (44).

Several studies on SpA evidenced that the entheses most commonly affected were those in the distal part of lower limbs (42). The true explanation remains unknown, but anatomic and physiological factors, such as the major length of the tendon and increased risk of mechanical injury might play a role (20, 45). We have not found a similar predilection for lower limbs in HIV patients, thus suggesting that factors other than repeated micro-trauma could have a role.

Table VIII. Classification of the altered HCV and HIV joints based on SH, JE and PD.

	SH+ and/or SF-/PD+ (active synovitis)		SH+ and/or SF+/PD- (inactive synovitis)	
	HIV n=19	HCV n=82	HIV n=19	HCV n=82
RCj, n	-	11	3	20
II MCP, n	-	3	2	4
III MCP, n	-	4	2	5
Knee, n	2	10	6	9
Ankle, n	-	5	4	11
Total, n (%)	2 (10.5)	33 (40.2) *p*=0.01	17 (89.4)	49 (59.7) *p*=0.01

HIV: human immunodeficiency virus; HCV: Hepatitis C virus; SF: synovial fluid; SH: synovial hypertrophy; PD: power Doppler; RCj: radiocarpal joint; MCP: metacarpophalangeal.

Among the PDUS altered entheses, no significant differences emerged between HIV and HCV patients with regard to the involvement of single entheses and the individual detected alterations, with the only exception of power Doppler that was significantly abnormal in HIV compared to HCV. This finding highlights a greater inflammatory activity of the PDUS altered entheses in asymptomatic HIV patients compared to HCV. The follow-up of these patients will clarify whether the alteration of the power Doppler signal can represent a predictive index of the onset of clinical symptoms.

Also in the assessment of the joints, PDUS proved to be more sensitive than clinical examination in detecting synovial alterations. Interestingly, the frequency of subclinical synovitis was significantly higher in HCV patients than in HIV and in HC, and alterations of vascularisation and synovial hypertrophy were significant more frequent in HCV than in HIV joints, which highlights a greater inflammatory activity of the PDUS altered joints in asymptomatic HCV patients compared to HIV. Our results are in line with the study of Iagnocco *et al*., which have found a higher frequency of US subclinical synovitis in HCV patients in comparison with HC (46). Conversely,

in our study no significative difference emerged between HCV and HC in the prevalence of US enthesitis. From a speculative point of view, these data allow to hypothesise that the main target in HIV could be the entheses, while synovium seems the preferred target in HCV. More studies comparing HIV and HCV patients are needed to verify this issue. Noteworthy, unlike HCV, in HIV patients joints of lower limbs (knee and ankle) were more frequently involved than those of upper limbs (RCj, II and III MCP), which seems to further highlight the close link between HIV and SpA as discussed above (36).

A limitation of our study must be taken into account, namely the small number of patients enrolled. However, the inclusion criteria aimed at selecting patients free from treatment understandably limited the recruitment.

In conclusion, our preliminary study shows the high frequency of PDUS enthesitis in asymptomatic HIV patients, which highlights the close link between HIV and SpA. If confirmed by further studies on a larger number of patients, these results could allow to classify the commonly HIV associated musculoskeletal syndromes in the broad spectrum of SpA. Conversely, the higher frequency of PDUS synovitis in asymptomatic HCV patients highlights the greater affinity of HCV arthritis with rheumatoid arthritis. PDUS proved to be more sensitive than clinical examination in detecting subclinical involvement of entheses and joints. Signs and symptoms of entheses and joints involvement should be carefully looked for in asymptomatic a clinically silent HIV and HCV patients.

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