

Joint replacement for avascular necrosis in people living with HIV

Francesco Pisanu¹, Vito Fiore², Martina Corradi¹, Elisabetta Esposito¹, Ivana Maida³, Gianfilippo Caggiari¹, Corrado Ciatti¹, Andrea Fabio Manunta¹, Carlo Doria¹

¹Orthopedics and Traumatology Department, University of Sassari, Italy; ²Infectious Diseases Department, Sassari, Italy; ³Infectious Diseases Department, University of Sassari, Italy.

Abstract. Recently, the interest on multifocal avascular necrosis (AVN) among people living with HIV (PLWH) is rising. PLWH have an incidence of symptomatic AVN significantly higher than the general population. The chronic viral infection may induce a direct damage via necrotizing vasculitis, on the other hand the highly active antiretroviral therapy represents a probable risk factor as it can indirectly lead to multifocal necrosis. Regardless of etiopathology, the AVN management in PLWH is the same as in the general population. Depending on symptoms, stage, and location, the AVN can be treated conservatively or surgically, but in its final stages joint replacement is often the most appropriate therapeutic option. The safety and outcomes of such major orthopedic surgery in PLWH are debated topics. In agreement with the literature in our case series we observed, despite some complication, a significant pain relief and excellent recovery of function after hip replacements. Although increased complication rates, several other independent risk factors associated with HIV infection can act as confounding factors. These confounders must be taken into account both in clinical practice and in data analysis. This case-based review highlights the increasing incidence of AVN in PLWH, and emphasizes the safety and effectiveness of the prosthetic joint replacement in this population. (www.actabiomedica.it)

Key words: People living with HIV; avascular necrosis; highly active antiretroviral therapy; joint replacement; total hip arthroplasty

Introduction

Avascular necrosis (AVN) is an ischemic or cytotoxic necrosis of epiphyseal bone, responsible for a progressive destruction and collapse of bone architecture leading to an increased risk of fractures and secondary arthritis (1, 2).

AVN is a debilitating disorder which clinical picture depends on the affected bone and the stage of disease. Sudden pain is the presenting symptom in most of the cases while joint mobility, usually preserved in early stages, progressively deteriorates in advanced stages.

The femoral head is the commonest site of affec-

tion (more than 75% of cases) (2) and being the cause of about 10% of all total hip prosthesis implanted in USA (3). The humeral head is the second most common site for nontraumatic osteonecrosis after the femoral head (4). AVN can be unifocal or multifocal, underlining a possible systemic origin. Both indeed traumatic and non-traumatic conditions, many of which still unknown, can interrupt the blood supply to the bone. The only well recognized non-traumatic causes for AVN include corticosteroid treatment (5), alcoholism, SLE, hypertriglyceridemia, hypercholesterolemia, and hemoglobinopathies (6, 7).

Recently, the interest on multifocal AVN among people living with HIV (PLWH) is rising. PLWH

have an incidence of symptomatic AVN ranging from 2.5 to above 100 times higher than the general population (5). Highly active antiretroviral therapy (HAART) has been studied as probable risk factor.

Numerous speculations on AVN pathogenesis among PLWH have been proposed. On one hand the chronic viral infection may induce a direct damage via necrotizing vasculitis, on the other the protease inhibitors (PIs) may indirectly cause hyperlipidemia, conducting to multifocal necrosis (8) (9). Furthermore, several studies highlighted a significant correlation between tenofovir disoproxil fumarate, the association of AZT/LPV/RTV and necrosis. However, AVN was widespread among PLWH even before such therapies were introduced (5).

Regardless of etiopathology, the AVN management in PLWH is the same as in the general population. Depending on symptoms, stage, and location, the AVN can be treated conservatively or surgically (1) (10), but joint replacement is likely the final step in the pathway for most AVN involving hip, shoulder and knee joints. The safety and outcomes of such major orthopedic surgery in PLWH has been previously discussed in literatures. Although increased complication rates have often been reported (11), in many studies several other independent risk factors were associated with HIV infection (e.g. hemophilia).

The safety of prosthetic surgery in HIV patients is demonstrated by a study showing a limited number of early (<6 weeks) and late (> 6 weeks) complications, such as superficial or deep infections, venous thrombosis, pulmonary embolism (11). In the past it was assumed an increased risk of hip prosthetic dislocation in PLWH, nevertheless this risk seems to be more related with the greater functional demands of these patients, on average younger than the general population undergoing prosthetic replacement (12).

Our aim is to describe our experience with 3 cases of multifocal AVN in PLWH.

Patients and methods

We retrospectively reviewed 3 PLWH attending to our ward for AVN. Data on medical history, HAART, and viro-immunological profile were col-

lected from patients' medical records, as well as surgical treatment and outcomes. Being people who inject drugs (PWIDs) was defined as drug injection also in the past. Alcohol consumption was classified in light (female <20 g/d, male <40 g/d), moderate (female 20–40 g/d, male 40–60 g/d), or severe (female >40 g/d, male >60 g/d), according to the well-known WHO definitions. Hyperlipidemia was defined as total cholesterol >200 mg/dl. Smoking was reported in pack-years. AVN staging was conducted according to Ficat and Arlet classification (1) (13). Post-surgical improvement was evaluated with Harris Hip Score (14), and Constant score (15) for shoulder replacement.

Results

Overall, 3 patients were sent to our ward. All of them reported bilateral disabling groin pain and severe hip functional limitation. One patient also experienced deep pain and severe impairment in both shoulders as long as an increasing pain and swelling bilaterally in the ankles. In the first two cases radiological results confirmed diagnosis of bilateral AVN of the femoral head (AVNFB), associated with bilateral asymptomatic osteonecrosis of the distal femur and proximal tibia in one of them. In the third case, imaging confirmed a bilateral AVNFB and AVN of both shoulders and ankles. All the patients were PWIDs, nobody had hemophilia.

Patients' medical history and baseline characteristics have been reported in table 1.

COPD: Chronic obstructive pulmonary disease; CVD: cardiovascular diseases; AIDS: Acquired Immuno-Deficiency Syndrome; HAART: highly active antiretroviral therapy; DRV/r: darunavir/ritonavir; TAF/FTC: tenofovir alafenamide/emtricitabine; EVG/COBI: elvitegravir/cobicistat; DTG: dolutegravir; 3TC: lamivudine; TDF: tenofovir disoproxil fumarate; PIs: protease inhibitors.

Case 1

The first patient (65 years old man, living with HIV for over 20 years, good compliance to antiretroviral therapy, danuravir and ritonavir + tenofovir alafenamide at the time of surgery), was a former

Table 1. Baseline characteristics of 3 patients living with HIV treated for avascular necrosis

Variable	Case 1	Case 2	Case 3
Sex	Male	Female	Female
Age	65	56	54
Comorbidities			
COPD	yes	yes	no
CVD	yes	yes	no
Active liver diseases	cirrhosis	cirrhosis	no
AIDS diagnosis	yes	yes	yes
Late presenter	yes	yes	yes
HIV-RNA	Not detected	57,000 cps/ml	Not detected
CD4+ nadir	38 cells/mm ³	8 cells/mm ³	190 cells/mm ³
Current HAART	DRV/r+TAF/FTC	EVG/COBI/TAF/FTC	DTG+3TC
Previous TDF use	>5 years	>5 years	>5 years
Previous PIs use	>5 years	>5 years	<5 years
Total cholesterol	291 mg/dl	362 mg/dl	276 mg/dl
Alcohol consumption	Moderate	Severe	Moderate
Smoking	Former	1 pack-year	0.5 pack-year

**Figure 1.** CT Symmetrical medullary lesion surrounded by a serpiginous sclerotic border in both knees. Remarkable cranialization of the joint line of the left knee.

smoker (2 pack-years until the year before onset of AVN symptoms) and PWID. The past medical history was significant for COPD, hypertension, paroxysmal AF, and surgery for thoracic aortic aneurysm (2011). The patient referred a deep bilateral hip pain from about one year and a sudden worsening of pain and severe functional limitation to the left side. Radiographs and CT showed: a) left femoral head flattening without significant osteoarthritis signs (AVNFIH stage III by Ficat classification) b) focal radiological changes with sclerotic and cystic lesion without deformities of the right femoral head (Ficat II). He underwent left total hip replacement and, one year later, right total hip replacement due to a contralateral progressive and severe symptomatology associated with radiographic progression of the AVN (Ficat III). In both hospitalizations, the inflammation markers were slightly increased without any sign of acute infection.

Case 2

The second patient (56 years old woman, HIV affected from over 20 years, low adherence to HAART, elvitegravir/obicostat/emtricitabine/tenofovir alafenamide at the time of surgery), was smoker (1 pack-year), and active PWID. Medical history was significant for COPD, previous HCV-related liver disease and anxiety attacks. She was first referred for orthopedic attention suspecting septic arthritis of the left knee. She complained severe functional impairment of left lower limb; a CT scan showed the total disruption of the epimetaphyseal bone structure around both knees (fig 1).

However, any infectious condition was rejected through the clinical and imaging examination and a benign asymptomatic bilateral bone infarction was diagnosed to the knees instead (fig 2). Furthermore, the pelvic X-Ray showed a dramatic bone resorption evocative for both advanced AVN to the left femoral head (stage IV by Ficat classification) and septic hip arthritis (fig 3).

The infectious etiology was excluded by normal inflammatory markers and then, during total hip replacement (May, 2020), by intraoperative macroscopic aspects and histological specimens. Before admission, her complete blood count (CBC) was normal with only a slight decrease in the number of WBC ($2.93 \times 10^3/\text{microL}$) which improved during hospitalization.

Case 3

The third patient was a 54 years-old woman, living with HIV from more than 10 years, smoker (0.5 pack-years) and PWID, no alcohol consumption was reported. She was affected by depressive syndrome. The patient attended our clinic for the first time in 2016, complaining worsening groin pain. Patient had good HAART compliance: she was in treatment with



Figure 2. MR PDW_TSE_spair coronal (a,b) and sagittal (c) images showing medullary metaphyseal bone infarct: central signal of normal marrow and serpiginous peripheral hyperintense signal. Peripheral low signal in T1W_TSE (d).



Figure 3. Articular destruction due to collapse of the left femoral head and acetabular massive bone resorption (stage IV of Ficat's classification)

Dolutegravir and Lamivudine since before AVNFH presentation. In November 2016 she underwent left THA then, during the following 5 years, she sought for orthopedic attention several times: in June 2017, right THA was performed; in September 2018, the patient started complaining deep pain in the shoulders; an X-ray and MRI were performed resulting in bilateral shoulders osteonecrosis with bone remodeling signs and no collapsed areas of the heads (Fig 4); one month later, considering the normal shape of the humeral head, the patient underwent a joint preserving surgery on the left shoulder (non-vascularized bone grafting) (Fig 5a). AVN and related pain worsening led to left reverse shoulder prosthesis (RSP) in 2019 (Fig 5b). After a couple of months, a wound revision surgery was indicated due to an impaired wound healing. Intraoperative swabs resulted in non-pathological tissue or infection signs. In June 2020, the patient underwent a right RSP (Fig. 5c) and then, after two months (August 2020), a conversion to hemiarthroplasty (Fig 5d) as a salvage procedure (16) due to an early glenoid loosening. Finally in March 2021, the patient came back to our attention because of a right shoulder anterior instability which was treated by performing a surgical correction of insufficient head retroversion; even in this case, surgeon found soft tissue spreading between the implant's components and samples were collected in order to analyze them histologically (normal granulation tissue was confirmed by micro-

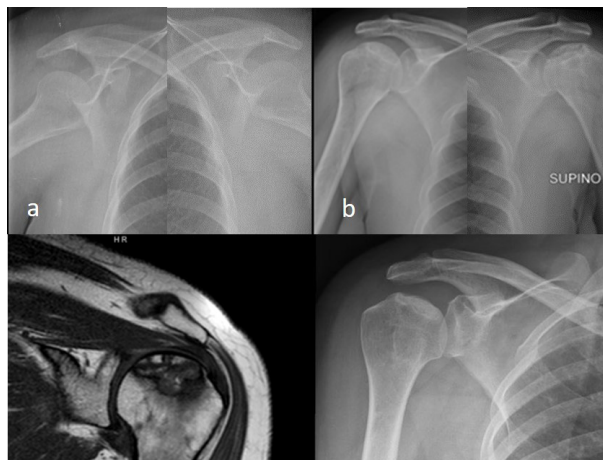


Figure 4. 2015 normal radiographs (a) and 3 years later, (b) crescent sign in both the humeral heads; (c) MR T1_TSE of right humerus with precollapsed stage of AVN (2018) and (d) left humeral head collapse (2020).

scopic examination). At the time of the last consult, the patient experienced severe bilateral ankles pain and swelling; a color doppler ultrasound scan excluded any vascular complications, while the radiographs showed a worsening in the well-known AVN pattern (Fig 6).

Patients' outcomes

Excellent radiographic results were observed in all hip replacements of this series (Fig. 7).

The first and the second patients reported post-operative improvements in terms of relief in pain, function, and ROM (pre-operative Harris Hip Score were 67 for the first patient and 71 for the second one, and postoperative score were respectively 91 and 95). For the first patient the intraoperative and postoperative blood loss was minimum, the second one needed a blood transfusion consequently a postoperative anemia. No complications from transfusion were observed. In both patients no thromboembolic complications and no immediate or

late infections occurred. It was not observed any major surgical complications and the surgical time was comparable to common THR duration. The average hospitalization was 9 days. The first patient recently died because of COVID-19 disease complications.

During the several hospitalizations, the third patient experienced complications such as: postoperative anemia, deep pain and a delay in the rehabilitation program especially linked to pain. ROM and articular function were gradually improved during years with the only exception of the right shoulder, which required a revision surgery due to instability in March 2021. After each of all surgeries the patient complained of dramatic pain (VAS 10/10), which totally resolved once another articulation was treated. Neither thromboembolic complications nor infections were detected. A delay in the wound healing required a revision surgery to the right shoulder (December 2020).

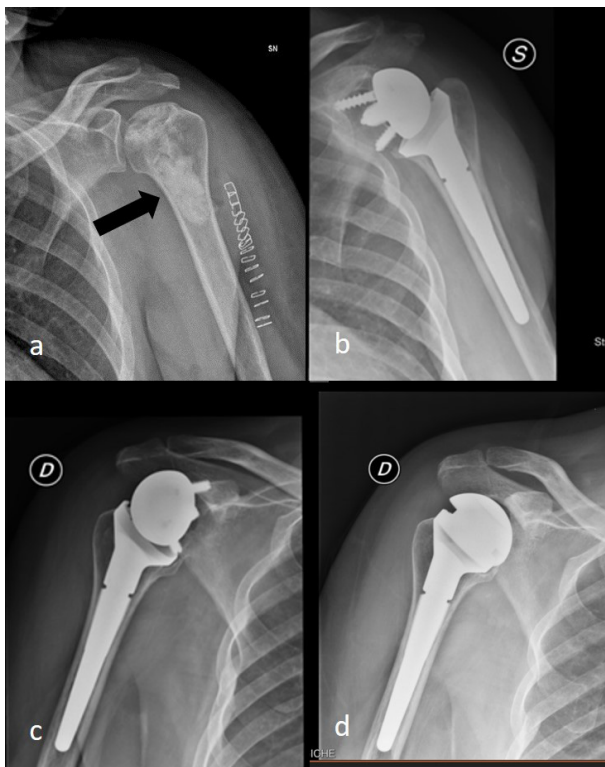


Figure 5. (a) non-vascularized bone grafting into the left proximal humeral metaphysis (black arrow) and (b) left RSA due to pain worsening; (c) right RSA, and (d) conversion to hemiarthroplasty as a salvage procedure due to glenoid loosening and insufficient bone stock.

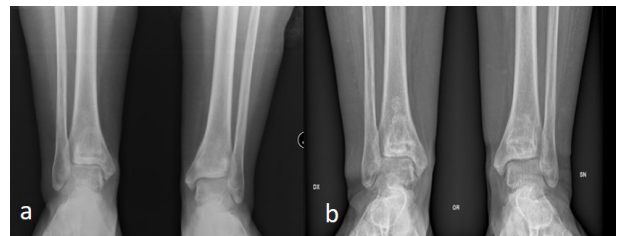


Figure 6. (a) paucisymptomatic early stage of bone infarction of the ankles (2015); in (b) after 3 years FU (2018), obvious medullary lesion with central lucency surrounded by shell-like sclerosis with a serpiginous border.

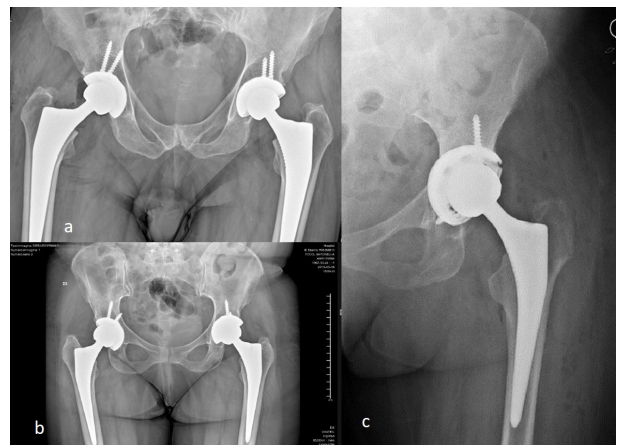


Figure 7. bilateral standard hip arthroplasty in case 1 (a) and case 3 (b); in case 2 the acetabular bone loss was addressed with an uncemented jumbo cup fixed with 3 screws; synthetic bone granules were used to supplement the bone stock.

At 4 and 3 years follow up the HHS were respectively 87 for the left hip and 73 for the right hip. Recently, at 4 and 5 years postoperative follow up, HHS lowered to 60 (left) and 46 (right), even if the pain domain score has remained stable (44 pts. left, and 30 pts. right). Indeed the overwhelming pain due to the worsening of the ankles' AVN drastically reduced the score in the HHS domain of function. Constant scores was 59 to the left shoulder (one year follow-up); the patient reports a subjective clinical and functional improvement on the right shoulder despite, at one month of follow-up, it has not yet been quantified with the Constant score.

Discussion

Osteonecrosis affects individuals leading, often, to progressive loss of function. Its incidence appears stable in the general population but it seems increasing among PLWH (17). As previously discussed, multiple risk factors have been well established. Moderate/severe alcohol consumption, smoking, hyperlipidemia, and corticosteroid use have been reported as major drivers in AVN among PLWH (17), as well as PIs and TDF use (both for current or past use) (18) (19). Also AIDS and lower CD4+ nadir have been found to be associated with AVN (20).

Our data are concordant with literature. In fact, all patients were smokers (one former), had hyperlipidemia, and were HAART experienced patients. Furthermore, they were all late presenters at the time of HIV diagnosis, and all had multiple treatment regimens, including PIs and TDF. Moreover, alcohol consumption was moderate-to-high in all patients.

Broadly speaking, depending on symptoms, stage, and location both surgical and non-surgical options are available for AVN management. In PLWH due to the common early presentation of a multifocal AVN, the rapid progression between the stages of the disease and the intense painful symptomatology (21) multiple joint replacement surgery is often necessary.

In this case series in agreement with the literature (10) we observed a significant pain relief and excellent recovery of function in joint replacement surgery, as already reported also in patients who are not PLWH and

in more complex surgical situations (22) (23). The poor score recorded with HHS in the third patient is misleading. Actually the overall HHS score is extremely influenced by factors unrelated to the hip prosthesis. In this specific case, the functional impairment is linked to the overwhelming pain due to the worsening of the ankles' AVN, drastically reducing the score in the domain of function (24). Indeed, the scores strictly related only with hip prosthetic joint (pain, deformity, and ROM) are stable and good among years.

In the third case despite a complicated postoperative course also the outcomes of shoulder replacement are fair. This satisfactory clinical and functional result even allowed the use of crutches, currently necessary for walking due to disabling pain in the ankles.

Obviously the results of prosthetic surgery, as well as those of bone healing, are influenced by the systemic environment (25). Despite increased complication rates have often been reported, several other independent risk factors associated with HIV infection can act as confounding factors. These confounders must be taken into account both in clinical practice and in data analysis. Concerns about dislocation risk and wear of prosthetic implant can be related with the greater functional demands typical of these patients; especially if we considered that PLWH are usually younger than the average population receiving a prosthetic joint. In conclusion, prosthetic joint replacement, with due consideration of all associated risk factors, ultimately appears to be a safe procedure in PLWH and as effective in improving QoL as in the general population of patients with AVN.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical review and approval were waived for this retrospective study.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Ficat RP. Idiopathic bone necrosis of the femoral head. Early diagnosis and treatment. *J Bone Joint Surg Br* 1985; 67(1): 3-9. doi: 10.1302/0301-620X.67B1.3155745. PMID: 3155745.
2. Pijnenburg L, Felten R, Javier RM. Ostéonécroses aseptiques, une revue générale des ostéonécroses de la hanche, et au-delà [A review of avascular necrosis, of the hip and beyond]. *Rev Med Interne* 2020; 41(1): 27-36. French. doi: 10.1016/j.revmed.2019.10.332. Epub 2019 Nov 10. PMID: 31722835.
3. Seijas R, Sallent A, Rivera E, Ares O. Avascular Necrosis of the Femoral Head. *J In-vest Surg* 2019; 32(3): 218-9. doi: 10.1080/08941939.2017.1398282. Epub 2017 Dec 29. PMID: 29286832.
4. Hernigou P, Hernigou J, Scarlat M. Shoulder Osteonecrosis: Pathogenesis, Causes, Clinical Evaluation, Imaging, and Classification. *Orthop Surg* 2020; 12(5): 1340-9. doi: 10.1111/os.12788. Epub 2020 Oct 4. PMID: 33015963; PMCID: PMC7670135.
5. Reddy R, Daftary MN, Delapenha R, Dutta A, Oliver J, Frederick W. Avascular necrosis and protease inhibitors. *J Natl Med Assoc* 2005; 97(11): 1543-6. PMID: 16334502; PMCID: PMC2594929.
6. Mankin HJ. Nontraumatic necrosis of bone (osteonecrosis). *N Engl J Med* 1992; 326(22): 1473-9. doi: 10.1056/NEJM199205283262206. PMID: 1574093.
7. Pisanu F, Pes M, Caggiari G, et al. Total hip arthroplasty: Concerns and precautions in sickle-cell trait. *J Orthop* 2019; 18: 117-120. doi: 10.1016/j.jor.2019.11.038. PMID: 32021016; PMCID: PMC6994769.
8. Adarraga MD, Sanchez-Martínez F, Caracuel MA, Escudero A, Collantes E. A Case of Multiple Osteonecrosis in a Patient with HIV: Effect of Joint Lavage. *J Clin Rheumatol* 2000; 6(1): 41-4. doi: 10.1097/00124743-200002000-00007. PMID: 19078448.
9. Brown P, Crane L. Avascular necrosis of bone in patients with human immunodeficiency virus infection: report of 6 cases and review of the literature. *Clin Infect Dis* 2001; 32(8): 1221-6. doi: 10.1086/319745. Epub 2001 Mar 26. PMID: 11283813.
10. Kim-Orden M, Kody B, Monti K (2017) Algorithm for Treatment of Hip and Knee Osteonecrosis: Review and a Presentation of Three Example Cases. *J Rheum Dis Treat* 3: 053. doi.org/10.23937/2469-5726/1510053
11. Graham SM, Lubega N, Mkandawire N, Harrison WJ. Total hip replacement in HIV-positive patients. *Bone Joint J* 2014; 96-B(4): 462-6. doi: 10.1302/0301-620X.96B4.33213. PMID: 24692611.
12. Ortiguera CJ, Pulliam IT, Cabanela ME. Total hip arthroplasty for osteonecrosis: matched-pair analysis of 188 hips with long-term follow-up. *J Arthroplasty* 1999; 14(1): 21-8. doi: 10.1016/s0883-5403(99)90197-3. PMID: 9926948.
13. Jawad MU, Haleem AA, Scully SP. In brief: Ficat classification: avascular necrosis of the femoral head. *Clin Orthop Relat Res*. 2012; 470(9): 2636-9. doi: 10.1007/s11999-012-2416-2. PMID: 22760600; PMCID: PMC3830078.
14. Nilsson A, Bremander A. Measures of hip function and symptoms: Harris Hip Score (HHS), Hip Disability and Osteoarthritis Outcome Score (HOOS), Oxford Hip Score (OHS), Lequesne Index of Severity for Osteoarthritis of the Hip (LISOH), and American Academy of Orthopedic Surgeons (AAOS) Hip and Knee Questionnaire. *Arthritis Care Res (Hoboken)* 2011; 63 (Suppl 11): S200-7. doi: 10.1002/acr.20549. PMID: 22588745.
15. Constant CR, Murley AH. A clinical method of functional assessment of the shoulder. *Clin Orthop Relat Res* 1987; (214): 160-4. PMID: 3791738.
16. Glanzmann MC, Kolling C, Schwyzer HK, Audigé L. Conversion to hemiarthroplasty as a salvage procedure for failed reverse shoulder arthroplasty. *J Shoulder Elbow Surg* 2016; 25(11): 1795-802. doi: 10.1016/j.jse.2016.03.011. Epub 2016 May 31. PMID: 27260994.
17. Bayard C, Ledergerber B, Flepp M, et al. Associations Between Antiretroviral Treatment and Avascular Bone Necrosis: The Swiss HIV Cohort Study. *Open Forum Infect Dis* 2017; 4(4): ofx177. doi: 10.1093/ofid/ofx177. PMID: 29026869; PMCID: PMC5632527.
18. Permpalung N, Ungprasert P, Summachiwakij S, Leeaphorn N, Knight EL. Protease inhibitors and avascular necrosis: a systematic review and meta-analysis. *Int J Antimicrob Agents* 2014; 44(2): 93-5. doi: 10.1016/j.ijantimicag.2014.02.011. Epub 2014 Mar 28. PMID: 24726526.
19. Green KR, Hernandez-Jimenez JM, Isache CL, Jacob R. Avascular necrosis: a growing concern for the HIV population. *BMJ Case Rep* 2018; 2018: bcr2017221678. doi: 10.1136/bcr-2017-221678. PMID: 29880618; PMCID: PMC6011430.
20. Borges ÁH, Hoy J, Florence E, et al. Antiretrovirals, Fractures, and Osteonecrosis in a Large International HIV Cohort. *Clin Infect Dis* 2017; 64(10): 1413-21. doi: 10.1093/cid/cix167. Erratum in: *Clin Infect Dis* 2017 Oct 15; 65(8): 1431-33. PMID: 28329090.
21. Mazzotta E, Agostinone A, Rosso R, et al. Osteonecrosis in human immunodeficiency virus (HIV)-infected patients: a multicentric case-control study. *J Bone Miner Metab* 2011; 29(3): 383-8. doi: 10.1007/s00774-010-0245-5. Epub 2011 Jan 22. PMID: 21258827.
22. Pisanu F, Andreozzi M, Costagli F, et al. Resumption of physical activity and sport after knee replacement. *J Orthop* 2020; 20: 247-50. doi: 10.1016/j.jor.2020.01.033. PMID: 32082037; PMCID: PMC7019124.
23. Pisanu F, Andreozzi M, Fiori E, et al. Surgical management of hip prosthetic failure in metallosis: A case series and literature review. *J Orthop* 2021; 28: 10-20. doi: 10.1016/j.jor.2021.10.002. PMID: 34707335; PMCID: PMC8521220.
24. Manca A, Pisanu F, Ortu E, et al. Isokinetic cross-training

- effect in foot drop follow-ing common peroneal nerve injury. *Isokinetics and Exercise Science* 23 (2015): 17-20. doi: 10.3233/IES-140559
25. Caggiari G, Ciurlia E, Ortu S, et al. Osteochondral avulsion fracture of the postero-medial tibial plateau. *Trauma Case Rep* 2020; 25: 100281. doi: 10.1016/j.tcr.2020.100281. PMID: 31956689; PMCID: PMC6957839.

Received: 15 November 2021

Accepted: 23 December 2021

Correspondence:

Corrado Ciatti, MD

Orthopedics and Traumatology Department,

University of Sassari,

Viale San Pietro, 07100 Sassari Italy

E-mail: dadociatti@icloud.com