Postoperative outcomes in total hip arthroplasty following femoral head avascular necrosis in HIV-positive patients

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Abstract. Background: Few clinical studies have been published reporting the clinical outcomes of total hip replacement (THA) in HIV-positive patients affected by femoral head avascular necrosis (AVN) often with controversial results and often without any correlation with the immunological patient status. Our study aim is to retrospectively review the outcome of a HIV-positive patient series. Material and Methods: 24 THAs performed between 2007 and 2017 were assessed in the study. All patients have been classified with Charlson Comorbidity Index (CCI) and the CDC (Center for Disease Control and Prevention) HIV classification. At the latest follow-up each patient have been evaluated using Harris Hip Score (HHS), WOMAC score, a numerical pain rating scale (NRS) and procedure-related complications were collected. Results: At a mean mean follow up of 96.41 months the mean WOMAC score was 91.66 and the mean Harris Hip Score was 86.77 with excellent results in 18 hips, good in 1 and poor in the 5. Post-operative complications were reported in 7 hips, 3 patients developed a periprosthetic joint infection (PJI) in patients with low CD4+ count and history of intravenous drug consumption. Conclusion: We registered a good outcome in HIV patient with femoral head AVN treated with Total Hip replacement. However, we reported a significant increase in complications and revision rate especially referred to PJI, in patient with history of intravenous drug consumption and low CD4+ count. The authors advocate further prospective multicentric studies with larger population in the future. (www.actabiomedica.it9

Key words: Osteonecrosis, avascular necrosis, femoral head, HIV, Hip Arthroplasty, Total Hip Replacement, complications

Background

Avascular necrosis (AVN) or osteonecrosis is a condition characterized by the ischemic subchondral bone death of because of a compromised arterial blood supply. This is an emerging complication in patients affected by Human Immunodeficiency virus (HIV) and typically localized at the femoral heads (1). The etiology of AVN associated with HIV is not well defined, but its incidence has increased since the advent of highly active antiretroviral therapy (HAART), in particularly with protease inhibitors (2).

HAART is not the only risk factor associated to AVN in these patients. HIV infection itself may be an independent risk factor because the frequent association with corticosteroid use, hypercholesterolaemia, hypertriglyceridaemia, smoking, alcohol excess, antiphospholipid antibodies and appetite stimulants such as megestrol acetate (3).

Total Hip Arthroplasty (THA) is the definitive and most effective surgical procedure in femoral head AVN even in high demand and young patients (4) despite several Authors reported poorer results compared to THA in primary arthritis (5,6). Likewise in
literature data are controversial about total hip replacement in HIV patient. In 2019 a meta-analysis pointed out an increased risk for both infections and revisions in HIV infected patients undergoing lower limb arthroplasty for any causes (7). However, these findings are based on poor quality evidence in a limited number of studies and need to be interpreted with caution (8).

In literature, few clinical studies have been published documenting the clinical outcomes of orthopedic surgeries in HIV-positive patients affected by femoral head AVN, often with controversial results. However, some Authors suggest that outcomes of primary THA for femoral head osteonecrosis in HIV-positive patients, despite longer operation times, is still a safe and efficient approach with a much lower complications incidence than previously reported in literature (9). Similarly Chokotho et al., assessing 12 HIV positive patients treated with THA because AVN, reported no early postoperative complications assuming that early response to arthroplasty surgery in AVN of the femoral head is equally good despite the HIV serological status (10).

The purpose of this study is to retrospectively review the outcome of a consecutive HIV-positive patient series affected by femoral head AVN treated with THA. Our goal is to determine if this type of intervention has good results in terms of clinical scores and acceptable risk for post-operative complications. All procedures have been performed in a single center by a single surgical team.

Materials and Methods

The study was carried out at ASST Fatebenefratelli Sacco University Hospital, Milan, Italy in the orthopedics and trauma department. Our hospital is equipped with a territorial reference center for infectious and tropical disease department and is also a regional reference center for HIV disease. From 2007 to 2017, 20 HIV-positive patients (25 hips) with femoral head AVN had been treated with total hip arthroplasty. Main reason for the surgical indication was an uncontrolled hip pain non-responsible with all the previous treatments, associated to a significant limitation in quality of daily life. The exclusion criteria to the study were: missing data regarding the immunological status at the surgical procedure time (THA), history of precedent hip trauma, absence of a follow-up, absence of clear radiological findings of AVN.

All patients co-morbidities have been registered and classified with Charlson Comorbidity Index (CCI) (11). This score classifies co-morbid conditions predicting mortality risk with a score ranging from 1 to 6 for 19 pathological conditions (including HIV-positivity/AIDS) and it is an easily applicable method for the preoperative comorbidities assessment in patients undergoing orthopedic surgery. From the database of our hospital we collect data regarding: report of AVN at Magnetic Resonance Imaging (MRI) (12), presence of bilateral AVN, surgical time and surgical approach used for the surgical procedure. Furthermore patients were assessed for: viral load (considering as undetectable a viral load lower than 50 copies/ml according the WHO/UNAIDS 2018 program) (13), CD4+ T-lymphocyte count (cell/l) and adherence to antiretroviral therapy according to the infectious disease specialist prescriptions. All patients have been classified according the CDC (Center for Disease Control and Prevention) classification (14). The revised CDC classification system for HIV-infected adolescents and adults categorizes persons on the basis of clinical conditions associated with HIV infection and CD4+ T-lymphocyte counts. The system is based on three ranges of CD4+ T-lymphocyte counts and three clinical categories and is represented by a matrix of nine mutually exclusive categories (Table 1). The CD4+ counts categories guide clinical and therapeutic actions in the management of HIV-infected patients (15) and have been used as criteria to proceed in elective surgery of HIV infected patients (16).

At the latest follow-up each patient has been evaluated using Harris Hip Score (HHS), WOMAC score, a numerical pain rating scale (NRS value: ranging from 0 to 10) and any significant inferior limb discrepancy (discrepancy ≥ 1.5cm) was registered. (17, 18, 19)

Complications were collected at the follow-up visits according to definitions and stratification advocated by The Hip Society including: periprosthetic joint infection, heterotopic ossification, bearing surface wear, osteolysis, implant loosening, cup-liner dissociations, implant fractures, re-operations, revisions,
Table 1. CDC classification system

| CDC classification system for HIV-Infected | CD4+ Cell count Categories | Cells/mcL | (A) Acute HIV, Asymptomatic | (B) Symptomatic | (C) AIDS-Indicator Conditions |
|------------------------------------------|--------------------------|-----------|-----------------------------|----------------|-------------------------------|
|                                          |                          | ≥ 500     | A1                          | B1             | C1                           |
| 1                                        |                          | 200-499   | A2                          | B2             | C2                           |
| 2                                        |                          | < 200     | A3                          | B3             | C3                           |

CDC 1993 Revised Classification System for HIV Infection from [https://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm](https://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm).

These categories correspond to CD4+ T-lymphocyte counts per microliter of blood and the clinical categories of HIV infection are defined as follows:

**Category A**

Consists of one or more of the conditions listed below in an adolescent or adult (greater than or equal to 13 years) with documented HIV infection. Conditions listed in Categories B and C must not have occurred.

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

**Category B**

Consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical Category C and that meet at least one of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Examples of conditions in clinical Category B include, but are not limited to:

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5 C) or diarrhea lasting greater than 1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy

**Category C:**

Includes the clinical conditions listed in the AIDS surveillance case definition (Appendix A). For classification purposes, once a Category C condition has occurred, the person will remain in Category C.

readmissions, deaths (20). All patients were routinely followed-up according to the department protocol for total joint replacement surgery. Outpatient clinical and radiologically follow-up were performed at 3, 6 and 12 months in the first post operative and subsequently at annual intervals. However, for the study all patients were contacted to perform a study-dedicated clinical evaluation. In the reassessment, the last available X-ray performed was also evaluated.

A statistical analysis was carried out using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).
Table 2. Demographic data and Outcomes (NRS, Harris Hip Score, WOMAC Score)

| Demographic data | Mean       | Standard deviation | Range (Min-Max) |
|------------------|------------|--------------------|-----------------|
| Age (yy)         | 45.95      | ± 8.91             | 30-69           |
| M:F ratio        | 2.1:1.     | -                  | -               |
| CCI Score        | 10.04      | ± 4.03             | 6-19            |
| CD4+ count (cells/mm3) | 685       | ± 364              | 110-1.135       |
| CD4+ (%)         | 29.02.     | ± 9.02             | 12-39           |
| Viremia          | <37        | -                  | 0               |
| Length of stay (days) | 9.16     | ± 4.5              | 5-19            |

Outcomes

| Mean       | Standard deviation | Range (Min-Max) |
|------------|--------------------|-----------------|
| VAS        | 0.9                | ± 1.62          | 0-4             |
| Harris Hip Score | 86.77     | ± 21.24         | 20.4-99.5       |
| WOMAC score | 91.66      | ± 13.96         | 57.3-100        |

Results

Of the 20 patients 19 were eligible for the study because 1 patient lost at the follow up had been excluded. There were 13 (68.4 %) male patients and 6 (31.6%) females with a M:F ratio of 2.1:1. We report that 2 of the male patients had been undergone to Male-to-Female sex reassignment surgery associated to hormonal therapy previously hip arthroplasty.

The mean age was 45.95 years (range: 30-69; SD±8.91) with 6 (31.6%) patients with a proved intravenous drug consumption history. All patients have a HIV RNA detection below 37 copies/ml. The mean CD4+ count was 685 cells/mm³ (range: 110-1135; STD±364) with a mean CD4+ percentage of 29.02 (range: 12-39; STD ± 9.02) and all the patient were in Highly Active Anti Retroviral Therapy (HAART) at the surgical procedure period. All patients followed antiretroviral therapy according the prescription the last infectious disease visit during follow-up. We also considered patients who reported behaviors such as skipping doses, taking medications at incorrect times or at incorrect doses as poor adherence. We registered 3 (17.8%) patients who reported poor adherence behavior to therapy during follow-up period, all of them referred skipping dose.

In terms of CDC classification 8 (42.1%) patients were in A1 category, 2 (10.5%) for B1 and 1 (5.3%) patient’s for both B2 and B3, 5 (26.3%) patients in C1, 2 (10.5%) in C2 and 1 (5.3%) in C3.

The mean pre-operative Charlson Comorbidity Index was 10.04 (range:6-19; SD: ± 4.03). The mean surgical time was 116.5 min (range 55 - 170 min; SD±27min), the mean length of stay was 9.16 days (range 5-19; SD±4.5). (Table: 2)

Six (31.6%) patients suffered a bilateral disease and 5 (26.3%) patients underwent to a bilateral procedure. Twenty (83.3%) of the 24 surgical procedure were performed with an antero-lateral approach, 3 (12.5%) with a direct anterior approach and 1 (4.2%) with a postero-lateral approach. (Table: 3)

The mean last follow up assessment occurred at a mean of 96.41 months postoperatively (range:15-212;
STD: ± 47.95). At the last follow up the mean Numeric rating Scale (NRS) was 0.9 (range: 0-4; SD ± 1.62), the mean WOMAC Score at last follow up was 91.66 (range: 57.3-100; SD: ±13.96) and the mean Harris Hip Score was 86.77 (range: 20.4-99.5; SD: ±21.24). According WOMAC score excellent results were observed in 18 (75.0%) hips, good in 1 (4.2%) and poor in 5 (20.8%) hips all occurring in patients referring post operative complications. Furthermore, we did not register any major limb length discrepancy (discrepancy > 1.5cm).

According to the CDC classification we registered a higher number of patients in category A1 (Table: 4) these patients belong to the clinical class

| CDC classification | Number of patients (%) | Complication registered: (number of patients) |
|--------------------|------------------------|---------------------------------------------|
| A1                 | 8 (42%)                | Squeezing:(1)                               |
|                    |                        | Post operative mobilization:(1)             |
| A2                 | 0                      |                                            |
| A3                 | 0                      |                                            |
| B1                 | 2 (11%)                |                                            |
| B2                 | 1 (5%)                 |                                            |
| B3                 | 1 (5%)                 | PJI: (1)                                   |
| C1                 | 5 (26%)                | Deficit SPE: (1)                           |
| C2                 | 2 (11%)                | PJI: (2)                                   |
| C3                 | 0                      |                                            |

Figure 1. Pre operative and post operative x-ray of a severe femoral head avascular necrosis treated with total hip replacement
A (Asymptomatic) with a CD4 + T white blood cell count greater than 500 cells/mm³. The second most represented category is that of C1. Patients in clinical category C have conditions defined as AIDS indicators by the CDC and a CD4 + T white blood cell count greater than 500 cells/mm³. All patient in the study belong to C category because the presence of neurotoxoplasmosis encephalopathy HIV-related.

The most represented comorbidity in the study was the concomitant HCV (Hepatitis C Virus) infection, present in 8 (42.1%) patients followed by neurotoxoplasmosis in 7 (36.8%) patients and liver disease in 6 (31.6%) patients. Only 3 (15.8%) patients have a single comorbidity (HIV infection only), 9 (47.4%) patients have from 2 to 4 comorbidities and 7 (36.8%) patients have 5 or more comorbidities.

Post-operative complications were reported in 7 (36.8%) patients and a total of 4 patients undergone to revision surgery. Three (15.8%) patients developed a periprosthetic joint infection (PJI): at 2 years from joint replacement in a 51-years old male (CCI=15 and CDC=C2) and at respectively at 11 and 5 years from implantation in two 51 and 37 years old females with respectively a CCI of 7 and 9 and a CDC classification of B3 and C2. All these patients referred history of drug abuse with poor adherence to HAART therapy in 2 of the 3 patients. Despite the higher prevalence of PJI in B and C categories of CDC classification, due to the low number of patients involved, we were unable to statistically analyze the association between PTJ and CDC clinical categories. However a trend towards an increased risk of PJI can be observed in patients with low CD4 + T lymphocyte numbers. Squeezing was reported in 1 case (male, 34yrs, CDC=A1). Despite a Harris Hip score of 91,8 and a WOMAC of 97,7. A female patient reported a traumatic periprosthetic fracture (Vancouver B2) at 4 years from the hip arthroplasty treated successfully with femoral stem revision. One patient (male, 41yrs, CCI=9, CDC=A1) underwent to an early cup revision because an unacceptable cup malalignment with a consequent early head dislocation). Another patient (male, 51 yrs, CCI=12, CDC=C1) reported a post operatively (anterolateral approach) peroneal nerve palsy recovered in one month after surgery.

Conclusion

In literature there are different study dealing with outcomes of total hip and knee arthroplasty in HIV-infected patients reporting often completely different results (9, 21, 22). In 2015 a study compared early outcome of HIV positive and HIV negative patient with AVN undergoing to THA, reporting that THA is still a safe and efficient approach in HIV positive patients despite a longer surgical time with a much lower complication incidence than previously reported (9). Similarly in 2016 a systematic literature review underlined how HAART therapy together to an associated comorbidities efficient control appears to lower the rate of PJI in HIV positive population (21). However in 2019 another systematic literature review reported a higher infections and revisions incidence in HIV infected patients undergoing to lower limb arthroplasty (22). Nevertheless in literature there are few studies specifically addressing the outcomes of THAs for femoral head AVN in HIV-positive patients even because the objective difficulties to enrolled these patients often complicated by poor socio-economical status.

Looking at our results, we observed a majority of males with a ratio of 2,1 male to 1 female (68% males and 32% females), with a mean age of 45.9 years with an evident younger age and male predominance compared to literature. In 2017 Singh et al. assessing 2271 patients undergoing THA in AVN not specifically HIV infection related, reported a mean age of 55 years (range: 46–64) old with an average of male patients of 57,5% (5). We easily explained the higher presence of younger male patients in our series to the proved higher prevalence of HIV infection in relatively young male population (23).

In a 2017 Singh et al. reported a worst outcome following THA in patient with femoral head AVN compared to primary arthritis referring a 90-day mortality of 0.7%, a surgical site infection of 1.2% and revision at any time during the follow-up of 3.1% vs. 2.4% (5). Ancellin et al in 2019 reported no difference in THA survivorship between AVN and osteoarthritis at 10 years follow-up with similar outcomes but an increased complication rate in the AVN group (24). Likewise in our study we reported, at the latest follow-up, a good
outcome both in terms of WOMAC score (mean value of 91.66) and Harris Hip Score (mean value with 87.8) with excellent results (HHS>90) in 18 (75%) hips and poor (HHS< 70) in the last 6 (25%) hips totally comparable to other reports in literature assessing THA in femoral head AVN.

A recent study suggests that the outcome of THA in HIV positive patients is not worse than that of HIV negative patients (25). Falakassa in a 2014 retrospective cohort study at a mean 14 months follow-up concluded that that well controlled HIV patients on HAART therapy are at similar risk of PJI as the average population (26). In our study we registered 7 (36%) patients who encounter a complication, according The Hip Society classification, during the follow-up period with a significant high incidence in periprosthetic joint infection (15%) making at least questionable the assumption of a comparable complication rate to the HIV negative population undergoing to THA. However looking carefully to each complication, 4 of these (squeezing, periprosthetic fracture, peroneal nerve palsy and cup malalignment) were totally independent to HIV patient status leaving only the higher rate of PJI. Furthermore, we specifically investigated the immunological status of these 7 HIV-positive patients with complications demonstrating in all these patients a viral load less than 37 copies/ml as an optimal target for HAART therapy.

Considering the CD4 counts in literature Guild et al. find that counts less than 300 cells/mm³ were associated with development of postoperative infection in HIV positive patients(27) and in our patients the mean CD4+ count in our patients was 544 cells/mm³ with a CD4+ percentage of 28,8%. However considering only the patients complicated by PJI, in accordance with literature, we found 2 of 3 patients with a CD4+ count less of 300 cells/mm³ (a female patient 43yrs with 110 cells/mm³ and a CCI=9 and a male patient, 51yrs with 257 cells/mm³ and a CCI=15) because a poor adherence to HAART therapy. Considering the CDC classification, despite an undemonstrated statistical correlation, because the small sample size, PJI were present only in patients included B and C categories. Furthermore all patients complicated by a PJI referred a previous intravenous drugs consumption history and orthopedic implant infection according to literature(28).

Our study presents some bias: it was a retrospective study without a control group dealing with different implants and different approaches. However, it is one of the biggest series in the developed countries with a mean follow-up of more than 90 months described in literature and performed in a single center equipped with a referral infectious disease department by a single orthopedic team.

In conclusion in our study we registered a good outcome in terms of Harris Hip Score and WOMAC score in HIV patient with AVN treated with Total Hip replacement. Likewise, we reported a significant increase in complications and revision rate especially referred to PJI in patient with HIV associated AVN compared to patient with AVN general population. Increased risk could be linked more to social behavior (intravenous drug abuse) or lower than 300 cells/mm³ CD4+ count because a poor adherence to HAART therapy than to HIV infection alone as single risk factor making at least questionable the indication to treat all these patients in not specialized centers. The authors advocate further prospective multicentric studies with larger population in the future considering difficulties to enroll these patients often with a high incidence of drug dependence and poor social status.

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.

Ethical approval: 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.

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Received: 26 May 2020
Accepted: 20 July 2020
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APPENDIX

Appendice A:

Conditions included in the 1993 AIDS surveillance case definition
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive*
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary* or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

*Added in the 1993 expansion of the AIDS surveillance case definition.