Human immunodeficiency virus in total hip arthroplasty

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Introduction

The prevalence of human immunodeficiency virus (HIV) patients undergoing total hip arthroplasty (THA) is increasing worldwide. HIV is a pandemic affecting over 35 million adults (prevalence 0.8%). The European Centre for Disease Prevention and Control reports that HIV transmission remains a ‘major public health concern’ with over two million people living with HIV in the European Region and 159,420 new diagnoses made in 2017 (see Table 1). There are an estimated 120,000 people living with HIV in the United Kingdom (UK). The rate of new diagnoses in the UK is 11.4 per 100,000 people, which is almost double the rate of most other countries in western Europe. Whilst in eastern Europe there is a burgeoning epidemic with 998,525 people living with HIV in Russia and 244,000 in Ukraine, alone. Furthermore, over half (53.1%) of those newly diagnosed in the European Region have a CD4+ T-cell count (CD4+) < 350 cells/mm³. HIV-infected patients are at a greater lifetime risk of requiring THA. The aetiology is multifactorial, with causative mechanisms related to both the disease itself and treatment with highly active

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Table 1. Global HIV statistics

| Region                         | People living with HIV | New infections in past year |
|--------------------------------|------------------------|-----------------------------|
| Middle East and North Africa   | 220,000                | 18,000                      |
| Asia and Pacific               | 5,200,000              | 280,000                     |
| Europe                         | 2,000,000              | 159,420                     |
| - United Kingdom               | 120,000                | 6,095                       |
| Eastern Europe and Central Asia| 1,400,000              | 130,000                     |
| - Russia                       | 998,525                | 105,844                     |
| United States (US)*            | 1,140,400              | 50,000                      |
| Latin America                  | 1,800,000              | 100,000                     |
| West and Central Africa        | 6,100,000              | 370,000                     |
| Eastern and Southern Africa    | 19,600,000             | 800,000                     |
| - South Africa                 | 7,200,000              | 270,000                     |
| - Nigeria                      | 3,100,000              | 210,000                     |
| - Kenya                        | 1,500,000              | 53,000                      |

*Latest statistics available from 2017, except US (2016).
Source: UNAIDS,1 ECDC,2 CDC.35
antiretroviral treatment (HAART). It is controversial whether HIV-positive patients are at higher risk for adverse THA outcomes; however, poor immune status has been linked to increased incidence of complications. A fundamental understanding and approach to the interaction of HIV and THA is critical.

The pandemic nature of HIV underlines the importance of global expenditure. Worldwide, US$21.3 billion was spent on HIV in 2017 and it is estimated that US$26.2 billion will be required for the acquired immunodeficiency syndrome (AIDS) response in 2020. Concurrently, the demand for THA is already high and continues to rise. Approximately 91,698 procedures were performed in England and Wales in 2017. There are over 300,000 cases being performed in the United States of America (USA) annually, and this is projected to increase by 173% to 572,000 procedures by 2030. Compounding this strain, hospital re-admissions up to 90 days after THA represent a massive economic burden on healthcare systems. The total annual cost for 90-day readmissions after THA is approximately US$477 million in the USA, alone. Approximately half of these re-admissions are due to medical co-morbidities and are unrelated to the joint replacement procedure itself.

Despite the development of several preventative measures, the annual incidence of peri-prosthetic joint infection (PJI) in THA is 1.17% and has a five-year mortality rate of 21.12%. The annual cost for revisions due to PJI was US$566 million in 2009 and is expected to increase to US$1.62 billion by 2020. There were 8,073 revisions and 3,045 re-revisions in England and Wales in 2017. PJI is the third most common indication for revision hip arthroplasties and may be a result of both modifiable and non-modifiable risk factors. Non-modifiable risk factors associated with an increased risk of infection include age, gender, race and chronic diseases such as obstructive pulmonary or kidney disease, coagulopathies and cirrhosis. Modifiable risk factors have been shown to prolong the length of hospital stay and add to both the complication and early revision rates. These factors include obesity, poor dentition, opioid use, smoking, diabetes, Staphylococcus aureus colonization and HIV.

A clustering of co-morbid risk factors may also exist in HIV-infected patients undergoing THA. Additionally, the 2018 International Consensus on Orthopedic Infections determined that HIV posed an independent risk for PJI. However, the significance was negated once HIV-infected patients were placed on HAART and optimized pre-operatively. It is therefore imperative to identify and optimize HIV-positive patients prior to surgery in order to decrease the strain on already heavily burdened healthcare systems globally. A fundamental understanding and approach to the interaction of HIV and THA is critical. Additionally, this narrative review serves to highlight crucial aspects of the peri-operative management of HIV-infected patients undergoing THA necessary to optimize outcomes and reduce complications.

**Association between HIV and THA**

The burden of THA will be compounded worldwide as the HIV pandemic spreads. Whilst HIV incidence steadily increases, global access to HAART for those infected has improved from 25% to 59% between 2010 and 2017. As a result of improved access to HAART, a decline of 52.7% in AIDS-related mortality globally has been seen in 2017 since its peak in 2004. People are living longer due to improved access to HAART and are subsequently developing chronic degenerative joint diseases. Both the HIV disease itself and HAART used to treat HIV have independently been linked to hip pathology eventually necessitating joint replacement. HIV-positive patients are more predisposed to developing avascular necrosis (AVN) of the hip and femoral neck fractures due to decreased bone mineral density (BMD). Furthermore, the incidence of AVN has increased since the advent of HAART.

HIV and HAART have been implicated by several epidemiological studies as causes of AVN. Femoral heads are most frequently involved in HIV- and HAART-related AVN. Reports have indicated that the incidence of femoral head AVN in HIV-infected patients may be 45- to 100-fold greater compared to the general population. HIV-infected patients with osteonecrosis require THA at a younger age than patients affected by osteoarthritis, and joint involvement is often bilateral (Fig. 1).

**Fig. 1** Anteroposterior (AP) view of a 37-year-old HIV-infected male patient with a CD4+ of 438 cells/mm³ and an undetectable VL on HAART with bilateral femoral head AVN.

Note. CD4+, CD4+ T-cell count; VL, viral load; HAART, highly active antiretroviral treatment; AVN, avascular necrosis.
HIV negatively impacts BMD and HIV-infected patients are 3.7 times more likely to be osteoporotic than non-infected patients. Subsequently, an increased risk of fragility fractures in HIV-infected patients exists, especially femoral neck fractures in males. Risk factors associated with low BMD include low CD4+ nadir and longer duration of HIV infection. With no sign of disease retraction and widespread improvements in access to HAART, patients for THA should be routinely screened for HIV.

Evaluation and optimization of immune status

Optimization of the patient’s immune status is essential in the management of HIV-infected patients undergoing THA. Immunocompromised patients and those with uncontrolled virological status need to be identified in order to minimize peri-operative complications. Serum markers of disease control are CD4+ and viral load (VL). These markers should be measured pre-operatively if no result is available within the previous three months. CD4+ is a surrogate marker of immune status and a CD4+ < 200 cells/mm³ confirms the diagnosis of AIDS. In patients with CD4+ < 200 cells/mm³ there is increased incidence, morbidity and mortality due to opportunistic infections. Antibiotic prophylaxis should be initiated for all patients with CD4+ < 200 cells/mm³. Latest guidelines recommend trimethoprim-sulfamethoxazole (TMP-SMX) as prophylaxis for opportunistic infections.

Viral load is a reliable marker of treatment efficacy and is primarily dependent on patient adherence to medication. Patients adherent to HAART should have an undetectable VL, which is approximately < 50–100 copies/mL. If after 6–8 weeks with strict treatment adherence, the VL is > 1000 copies/mL or there has been a decrease in VL of less than one log from baseline measurement, there is virological failure. Patients with virological failure should be referred to an infectious disease specialist for assessment and elective surgery should be postponed.

HAART: changing HIV from a terminal to a chronic illness

Latest guidelines recommend that HAART should be initiated in every patient with confirmed HIV infection, regardless of clinical stage and with any CD4+. This is especially important in patients awaiting elective THA. All first-line HAART regimens consists of a dual nucleoside reverse transcriptase inhibitor (NRTI) combination plus a third agent from a different drug class. Some of the most recent global and regional guidelines are shown in Table 2. Protease inhibitors (PIs) are regarded as the main drug class contributing to AVN of the hip. Additionally, tenofovir-containing drugs are implicated in the development of osteopenia. Interestingly, all first-line regimens worldwide include a tenofovir-containing agent (see Table 2). This may subsequently further add to the global burden of THA with femoral neck fractures and even revision THA as a consequence of periprosthetic fractures.

There is ongoing research into the development of more ideal pharmaceutical agents due to the multiple adverse effects caused by current HAART regimens. The renal and osteodegenerative adverse effects of tenofovir disoproxil fumarate (TDF) have resulted in the development of tenofovir alafenamide (TAF). TAF still causes renal injury and bone loss, although damage is less extensive.
than with TDF. The common metabolic side effects and high cost of PIs have led to the advent of integrase strand transfer inhibitors (InSTIs) as the preferred first-line regimen recommendation by the WHO. Standard practice in the USA and UK already includes InSTIs. Whilst over half the global prevalence of HIV (53%) is in eastern and southern Africa, these areas do not yet have access to InSTIs in public healthcare.

Pre-operative optimization

HIV can impact multiple systems and patients must be fully assessed for peri-operative risk stratification before THA. Non-AIDS-associated diseases commonly found in HIV-infected patients include cardiovascular disease, renal disease, liver disease, neurological complications and malignant conditions. Pre-operative evaluation of HIV-positive patients must include appropriate blood work-up including serum albumin, nutritional state and stage of immune deficiency syndrome. Studies indicate that post-operative complications in HIV-positive patients are primarily caused by resultant immunodeficiency rather than the operation itself. Therefore a thorough evaluation is imperative to avoid both anaesthetic and surgical complications and improve functional outcomes after THA.

Nutritional state

Nutritional state should be assessed in all HIV-positive patients with advanced disease as they are at risk for wasting and nutritional deficiencies. Hypoalbuminaemia is an independent risk factor for post-operative mortality in HIV-positive patients when compared to uninfected controls. Malnutrition is associated with several complications after THA, including delayed wound healing, persistent wound drainage with subsequent susceptibility to infection and prolonged hospital stay. Nutritional supplementation may be warranted if oral intake is inadequate and a dietician should be consulted.

Cardiovascular risk

Cardiovascular disease has become a significant cause of death in HIV-positive patients. Retrospective studies indicate an increased risk of coronary artery disease amongst HIV-positive patients when compared to HIV-negative controls, which may be related to ongoing chronic inflammation, despite viral suppression. Initiation of HAART has been shown to reduce cardiovascular risk peri-operatively. Concomitantly there are metabolic adverse effects of specific agents to consider. There is an increased prevalence of insulin resistance, diabetes mellitus and hypercholesterolaemia in HIV-infected patients on HAART. This may contribute to the increased risk of femoral head AVN and subsequently the increased demand for THA in HIV-positive patients. Thorough clinical examination for lipodysrophic changes and a fasting lipogram should be carried out on all HIV-positive patients for THA, especially if they are on a HAART regimen including a PI.

Pulmonary function

The prevalence of smoking is over 40% higher in HIV-positive patients and the likelihood of cessation is less than in the general population. This predisposes these patients to atherosclerotic processes as well as chronic pulmonary disease and post-operative pulmonary infections. Pulmonary function tests should be performed on all HIV-positive smokers to assess diffusion capacity prior to elective surgery. Furthermore, AIDS patients are at risk for invasive bacterial nosocomial pathogens and elective THA should be postponed to allow for effective immune reconstitution.

Adverse effects of HAART

There are many adverse effects of HAART agents and the regimen that the patient is taking must be noted. PIs and non-nucleoside reverse-transcriptase inhibitors (NNRTIs) have significant drug interactions with anaesthetic agents used for induction and sedation. TDF is nephrotoxic, and these patients will require a blood urea nitrogen (BUN) test to assess renal function, with or without a urine protein-creatinine ratio. Zidovudine (AZT) causes anaemia and neutropenia, and these patients will require a complete blood count (CBC) and white cell count (WCC) including differential count.

THA outcomes in HIV-infected patients

There are conflicting findings in the literature regarding functional outcomes in HIV-infected patients undergoing THA. Much controversy still exists regarding the relative safety and efficacy of THA in HIV-infected patients. Common knowledge previously suggested an increased risk of adverse outcomes, especially infective complications, as a consequence of HIV infection. However, the literary landscape may have been tainted by studies evaluating homogenous groups of HIV-positive patients including haemophiliacs and intra-venous drug users (IVDUs). Furthermore, the widespread implementation of access to HAART has decreased the morbidity of the disease. Unfortunately, many studies do not specify whether patients were receiving HAART or record the serum measurements of disease control to assess immune status. The details of several studies are outlined in Table 3. In order to analyse the available data we will assess the current literature according to study cohorts including haemophiliacs.
Haemophilia and HIV

Historically, outcomes of THA in HIV-infected patients have included both haemophiliacs and IVDUs and have demonstrated both a significantly high rate of late deep infections and poor outcomes. In a systematic review of 722 THAs from 25 research projects, Enayatollahi et al reported that PJIs occurred with far greater regularity in HIV-infected patients with haemophilia than in patients with HIV alone. The rates of PJI were 10.98% and 2.28%, respectively. However, the incidence of PJI in an era before HAART was as dramatic as 50%. A decreased incidence of infections in THA in HIV-infected patients has coincided with the introduction of HAART.

Pre-HAART era

HIV-infected patients not receiving HAART have demonstrated increased risks of adverse events. Parvizi et al found a high rate of complications in HIV-positive patients undergoing THA in which 80% of participants were not receiving HAART. This included 29% resulting in PJIs. The average CD4+ for the patients with PJI compared to the study population as a whole was 239 cells/mm³ and 523 cells/mm³, respectively. Similarly, Lehman et al found a PJI rate of 14.3% in their HIV-positive patients for THA, none of whom were receiving HAART.

and/or IVDUs and studies conducted before and after the peak in AIDS mortality due to poor HAART access.

Table 3. Summary of selected papers demonstrated outcomes of THA in HIV-infected patients

| Study                | Number of participants | HIV+ disease control assessment | Results | Comments |
|----------------------|------------------------|---------------------------------|---------|----------|
|                      |                        | HIV+ receiving HAART (%) | Mean CD4+ (cells/mm³) | Post-operative infection* rate (%) | Revision rate (%) | |
| Ragni et al (1995)²⁵| 66                     | N/A                            | N/A     | 15.1     | N/A      |
| Lehman et al (2001)²⁶| 29                     | 0                              | N/A     | 14.3 DJI | N/A      |
| Enayatollahi et al (2016)²⁷ | 293 non-HEM 341 HEM | N/A/NE                         | N/A     | non-HEM vs. HEM (2.28 vs. 10.98) N/A/NE |
| Parvizi et al (2003)²⁸ | 15                    | 20                             | 523     | 29 DJI   | 62       |
| Lubega et al (2009)²⁹ | 18                    | 40                             | 100     | 0        | 5.6      |
| Torrero et al (2012)³⁰| 13                    | 27                             | 100     | 0        | 0        |
| Issa et al (2013)³¹  | 34                     | 70                             | N/A     | HIV+ vs. HIV- (5.8 vs. 0.0) N/A |
| Capogna et al (2013)³²| 69                    | 138                            | N/A     | HIV+ vs. HIV- DJI (4.40 vs. 0.72) N/A |
| Graham et al (2014)³³| 29                    | 100                            | 489     | 0        | 0        |
| Falakassa et al (2014)³⁴| 24               | 100                            | 647     | 0        | 4.2      |
| Snir et al (2014)³⁵  | 31                    | 100                            | 444     | 2.4 DJI  | 7.3      |
| Lin et al (2014)³⁶   | 22                    | 372                            | 95      | HIV+ vs. HIV- DJI (9.1 vs. 2.2) N/A |
| Naziri et al (2015)³⁷| 9275                  | 2 656 696                      | N/A/E   | HIV+ vs. HIV-wound infection (0.7 vs. 0.2) N/A/E |
| Dimitriou et al (2017)³⁸| 11 431            | 6 504 755                      | N/A/E   | HIV+ vs. HIV- (7.6 vs 3.3) N/A/E |

Note. HIV+, HIV-positive patients; HIV-, HIV-negative patients; HAART, highly active antiretroviral treatment; CD4+, CD4+ T-cell count (in cells/mm³); HEM, haemophiliac; IVDU, intra-venous drug user; DJI, deep joint infection; OR, odds ratio; VL, viral load; UVL, undetectable viral load (< 50 copies/mL); THA, total hip arthroplasty; TJA, total joint arthroplasty.

N/A, not available – data not recorded or mentioned; N/AE, not available or evaluated routinely in all papers analysed.

*Post-operative infection refers to peri-prosthetic joint infection, unless otherwise specified as DJI or wound infection.
HAART era

Several studies have shown equivocal functional outcomes in HIV-positive patients controlled using HAART when compared to HIV-negative controls. In 2014, Graham et al. reported no cases, either early (< 6 weeks) or late (> 6 weeks), of superficial or deep infections, dislocations or venous thrombotic events in 43 THAs performed in 29 HIV-positive patients. This series also reported significant functional gains made post-operatively with significant improvements in the Harris Hip Scores. Naziri et al. compared the outcomes of THA in 9275 HIV-infected patients with THA those of 2.7 million uninfected patients from the Nationwide Inpatient Sample in the USA from 1998 to 2010. HIV-infected patients had rates of major and minor complications of 2.9% and 5.2% respectively, which significantly outweighed the respective rates of 2.7% and 4.8% in non-infected patients. Additionally, an extended length of hospital stay was also noted in the HIV-infected cohort.

In a systematic review of 6.5 million joints included in 21 articles, Dimitriou et al. reported that the incidence of PJI in HIV-infected patients was 7.6% and was significantly greater than in non-infected THA, where the rate was found to be 3.3%. The complication rates in these papers ranged from 0% to 46%.

Sadoghi et al. analysed worldwide registry data from Sweden, Norway, Finland, Denmark, Australia, and New Zealand to highlight that aseptic loosening was the most common cause of revision in THA and accounted for 55.7% of revision THAs. The third most common reason for revision was PJI. HIV does not seem to contribute to the prevalence of aseptic loosening.

The survival rate of THA in HIV-infected patients is comparable with non-HIV-infected patients at one and five years post-operatively. In an article evaluating prosthetic longevity at 10 years, Issa et al. concluded that no differences in survival existed between HIV-infected and non-infected patients. Novikov et al. reported that the vast majority (80%) of revision THA occurred within one year post-operatively, but that ultimately the revision rate was comparable with non-infected patients in their long-term review. It can be concluded that although functional outcomes for HIV-positive patients on HAART are equivalent to HIV-uninfected patients, a higher risk for PJI exists.

Elective surgery thresholds

Due to the increased demand for THA and the pandemic nature of HIV, it is imperative to consider whether thresholds should be advised for elective THA. A retrospective study by King, et al. comparing 30-day post-operative THA mortality in the USA observed that mortality was higher among 1641 HIV-positive patients compared with 3282 HIV-negative controls (3.4% vs. 1.6%). This study found a higher mortality in the HIV-positive group when compared to the control, regardless of CD4+, although a lower CD4+ was associated with higher mortality.

A threshold of CD4+ of 200 cells/mm³, which correlates with an overriding risk of major post-operative complications including PJI, has been postulated but has gone unproven. There is strong evidence to support earlier post-operative failures in HIV-positive patients, especially those with poor disease control. Serum markers should be routinely followed up as infection remains a significant risk, especially if the CD4+ decreases. Most articles did not correlate the incidence of complications with CD4+ rigidly or routinely. Dimitriou et al. recommended that THA could be performed in HIV-infected patients safely irrespective of the CD4+ count. Shah et al., however, argued that safe elective THA may demand a CD4+ in excess of 400 cells/mm³.

The importance of pre-operative VL may supersede that of CD4+. A high VL may indicate treatment failure and demand referral to an infectious disease specialist. In a retrospective study of over 5000 HIV-infected patients it was reported that a VL > 30,000 copies/mL was associated with a three-fold increased risk of post-operative complications. Shah et al. in their systematic review, recommended a VL < 50 copies/mL prior to elective surgery. HAART should be continued in all patients and strict compliance is essential. Non-compliance or treatment failure must be considered if follow-up investigations reveal dwindling CD4+ and/or rising VL.

Recommendations

1. All patients eligible for THA, especially those with unknown aetiologia, should be sent for routine HIV screening.
2. All HIV-positive patients for THA should be initiated on HAART if not on pre-existing treatment.
3. HIV is a multisystemic disease and infected patients are at increased risk for medical co-morbidities which must be assessed and optimized pre-operatively.
4. If a CD4+ and VL have not been performed within three months prior to THA, these serum markers should be repeated.
5. AIDS patients with CD4+ < 200 cells/mm³ should be initiated on antibiotic prophylaxis to avoid peri-operative infections.
6. HIV-infected patients compliant on HAART for at least 6–8 weeks with VL > 1000 copies/mL or a decrease in VL of less than one log from baseline measurement are failing treatment and should be referred to an infectious disease specialist physician.
7. Consideration to postpone HIV-positive patients for elective THA will allow for immune reconstitution with a CD4+ > 200 cells/mm³ and may prevent post-operative complications.
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