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AUTHOR(S)

Shane C O'Neill, Joseph M Queally, Anne Hickey, Kevin J Mulhall

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Outcome of total hip and knee arthroplasty in HIV-infected patients: A systematic review

Shane C. O'Neill,^{1,2}

Joseph M. Queally,^{1,3} Anne Hickey,²

Kevin J. Mulhall¹

¹Cappagh National Orthopaedic Hospital, Dublin, Ireland; ²Royal College of Surgeons, Dublin, Ireland;

³Addenbrooke's Hospital, Cambridge, UK

Abstract

Significant advances in the treatment of Human Immunodeficiency Virus (HIV) have occurred in recent times, with life expectancy now approaching the normal population. Therefore, patients with HIV will increasingly be undergoing joint replacement in the future, however concerns remain regarding the complications and outcome in this patient cohort. The aim was to assess the outcome of total hip and knee arthroplasty in HIV-infected patients. A systematic search of the literature using MOOSE reporting guidelines was performed to assess the outcome of hip and knee arthroplasty in HIV-infected patients. The primary outcome was infection. Secondary outcome was all-cause revision. The search yielded 552 results, of which 19 met the inclusion criteria, comprising 5,819,412 joint replacements. The overall quality of the studies was poor with significant heterogeneity between the studies. Infection and revision appeared to be more likely to occur in HIV positive patients compared to HIV negative patients. A subgroup analysis of four studies revealed a risk ratio of 3.31 and 2.25 for increase in infection and revision respectively in HIV positive patients. This systematic review and meta-analysis demonstrates an increased risk of infection and revision in HIV infected patients undergoing total hip and knee arthroplasty. However, these findings are based on poor quality evidence in a limited number of studies and need to be interpreted with caution. Further research should concentrate on large, well-designed, prospective studies, that control for co-morbidities and employ standardised outcome measures to allow for direct comparison.

Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus that affects approximately 36.9 million people worldwide.¹ HIV

infects immune cells and untreated can progress to Acquired Immunodeficiency Syndrome (AIDS) leading to collapse of the immune system and subsequent opportunistic infection. With the advent of antiretroviral therapy, the life expectancy of patients has dramatically improved to approximately 78 years.² HIV has now become a chronic, manageable disease. These patients now have a relatively normal life span and therefore will be affected by chronic joint degeneration comparable to the general population.

Initial studies on the outcomes of hip and knee arthroplasty in HIV infected patients revealed an alarmingly high revision and complication rate.^{3,4} These initial studies were completed before the widespread availability of Highly Active Antiretroviral Therapy (HAART) and often using specific patient cohorts with co-existing medical co-morbidities.⁵ There will be an increasing demand for joint arthroplasty in this patient group in the future, due to both their inherent increased risk of osteonecrosis and the normal incidence of joint degeneration in an ageing population.⁶ It is important that the outcome of total joint arthroplasty in the context of modern medical management for HIV is assessed.

The primary objective of this study is to systematically review and conduct a meta-analysis of the current literature regarding the outcome of total hip and knee arthroplasty in HIV infected patients.

Patients and Methods

The systematic review was conducted according to the MOOSE reporting guidelines for observational studies.⁽⁷⁾ The search strategy was developed in conjunction with an experienced librarian to minimise publication bias. The following databases were searched in April 2018; Medline and Embase from 1945 to present. The following search terms were used; "total joint arthroplasty"; "total hip arthroplasty"; "total knee arthroplasty"; "HIV" and "human immunodeficiency virus". Additionally, a hand search was performed of relevant studies for any additional suitable articles. The search was not restricted by language.

Two reviewers independently selected the studies to be included in the review. The title of each article was assessed and if deemed potentially relevant the abstract was reviewed to ascertain whether it met the criteria for full article retrieval. The article was then critically assessed as to whether it was eligible or ineligible for inclusion in the study based on the following predefined

Correspondence: Shane C O'Neill, Cappagh National Orthopaedic Hospital, Dublin, Ireland.

Tel.: +35318140400

E-mail: shaneconeill@rcsi.ie

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inclusion criteria: a) reported on total hip arthroplasty or total knee arthroplasty, in b) HIV-infected patients with c) a non-HIV-infected comparison cohort. Any disagreements between reviewers regarding study selection were resolved by discussion. A list of all excluded studies and reasons for exclusion was recorded.

Outcome measures

The primary outcome was infection. Secondary outcome was all-cause revision. The following data was extracted from each included article where available; author, study design, sample size, demographics, length of follow-up, type of arthroplasty, co-morbidities, infection, revision rate, mortality, complications, antibiotic use, HIV diagnosis, HIV treatment.

Methodological quality assessment

The Newcastle-Ottawa Scale (NOS) was used to critically appraise the quality of the cohort studies included in the analysis.⁸ The scale was designed to evaluate the quality of non-randomised trials such as cohort and case-control studies included in meta-analysis and to incorporate these quality findings in the interpretation of the meta-analysis results. The scale assesses each

cohort study according to selection, comparability and outcome. For cohort studies, it utilises a 9-point scale, with studies obtain a score of 5 or less considered to be of poor quality. Two reviewers independently applied the scale and assessed the methodological quality of each included study. Any disagreements were resolved by discussion.

Data analysis

Due to the inherent methodological and clinical heterogeneity of the included studies and the evolution of HIV infection and treatment over the study period, a narrative review of the results has been presented. The structure of the review is based on the suggested format of the Cochrane Collaboration handbook section 13.6.2.⁹ Due to the low incidence of outcomes of interest and difference in study design of included studies, outcome measures of total hip arthroplasty and total knee arthroplasty have been analysed together.

Forest plots with the pooling estimate suppressed have been included as suggested by the Cochrane Collaboration handbook section 13.6.2.4.¹⁰ The relative risk (RR) and confidence intervals (CI) have been calculated for each study reporting on the primary outcome, infection rate and the secondary outcome, all-cause revision rate. Statistical analysis has been performed using Review Manager 5.3 (RevMan) (v.5.3.5 The Cochrane Collaboration 2014). The sources of heterogeneity are described

and discussed. A subgroup analysis of studies using non-haemophilic cohorts was performed. These studies were all performed post introduction of HAART treatment for HIV and were carried out over a similar time period 1998-2014. These studies had less heterogeneity as compared to the other studies in the review and were considered to be of good quality, sufficient to perform a subgroup analysis. The subgroup analysis was performed using Review Manager 5.3 (RevMan) (v.5.3.5 The Cochrane Collaboration 2014). A subgroup analysis of the incidence of infection and all-cause revision was performed using a random-effects model and a pooled risk ratio was calculated and presented using a forest plot.

Results

A total of 552 potential studies were obtained relating to the outcome of hip and knee arthroplasty in HIV-infected patients (Figure 1). After the exclusion of duplicates, 412 records underwent screening for inclusion. Sixty-eight full text studies were assessed for eligibility. Forty-nine full text studies were excluded for the following reasons: Twelve had no HIV negative comparison cohort; twelve were review articles; eleven had inadequate outcome and patient characteristic reporting; seven had mixed non-arthroplasty surgical procedures in the

cohort; six included a cohort previously described in another study and one did not report on hip or knee arthroplasty. A total of nineteen studies met the inclusion criteria narrative synthesis. Four studies were included in the subgroup analysis.

Patient characteristics

A total of 5,819,412 joint replacements were analysed in this systematic review across nineteen included studies. The patient characteristics of the included studies are presented in Table 1.¹¹⁻¹⁹ The mean patient age ranged from 31 to 66.2.¹⁵⁻¹⁸ Eleven studies reported the mean age for the entire cohort.¹⁸⁻²⁸ Seven studies stated the mean age by HIV status only.^{11-13,15-17} The study by Powell *et al.* was the only study to report the mean age for the entire cohort and HIV positive and negative cohorts separately.²² Lehman *et al.* stated mean age for each of their study groups, however only the mean age of the HIV negative cohort was clearly stated.³ The study by Lin *et al.* (2013) did not report mean age data for the included study group. Age data for the initial cohort prior to exclusions were presented in groupings.¹⁴

The reporting of sex data was variable. Six studies provided sex data for the entire cohort and HIV positive and negative cohorts separately.^{12,13,15,17,22,28} Two studies reported data for the entire cohort only,^{20,25} with two studies only presenting data based on HIV status.¹⁶ Eight studies provided no

Table 1. Patient characteristics of included studies.

Authors & Year (Ref.)	Mean Age (years)			Sex (% Male)			HIV Status	
	Total	HIV +	HIV -	Total	HIV +	HIV -	HIV +	HIV -
Mahure <i>et al.</i> 2017 (11)	-	58.2	66.2	-	49.28	34.63	278*	136,604*
Zhao <i>et al.</i> 2015 (12)	-	35	42	69.8	85.7	57.1	28	35
Lin <i>et al.</i> 2014 (13)	-	49 +/-17.8	59.5 +/- 11.8	42.4	100	41.6	20	355
Lin <i>et al.</i> 2013 (14)	-	-	-	-	-	-	8229*	5672795*
Issa <i>et al.</i> 2013 (15)	-	48 (34-80)	43 (18-71)	58.7	67.6	54.3	34	70
Capogna <i>et al.</i> 2013 (16)	-	44.8 +/-10	64.3 +/-12.6	-	58	39	57	134
Tornero <i>et al.</i> 2012 (17)	-	44.3 +/- 9.1	47 +/- 11.1	80	84.6	77.8	13	27
Rodriguez-Merchan <i>et al.</i> 2011 (18)	36.5 (24-52)	-	-	-	-	-	21*	22*
Goddard <i>et al.</i> 2010 (19)	43 (25-70)	-	-	-	-	-	16	41
Lubega <i>et al.</i> 2009 (20)	52 (18-73)	-	-	56.9	-	-	14	28 + 16 ^{unk}
Solimeno <i>et al.</i> 2009 (21)	39 (20-71)	-	-	-	-	-	33	59
Powell <i>et al.</i> 2005 (22)	32.5 (20-74)	33 (20-61)	35 (26-74)	100	100	100	19	13
Silva <i>et al.</i> 2005 (23)	40.1 (17.5- 70.5)	-	-	-	-	-	60* (19 ^{neg})	30*
Norian <i>et al.</i> 2002 (24)	33.7 (22-67)	-	-	-	-	-	29	9
Lehman <i>et al.</i> 2001 (3)	-	-	39 (33-45)	-	-	-	23	6
Thomason <i>et al.</i> 1999 (25)	31 (15-49)	-	-	93.3	-	-	12 (11 ^{neg})	3 ^{unk}
Vastel <i>et al.</i> 1999 (26)	40.8 (22-63)	-	-	-	-	-	12	9
Lofqvist <i>et al.</i> 1996 (27)	46 (22-65)	-	-	-	-	-	4 (3 ^{neg})	7
Kelley <i>et al.</i> 1995 (28)	38 (15-73)	-	-	100	100	100	16 (12 ^{neg})	11 ser/ukn

*Reported as joints; - not stated; unknown HIV status; ser/unksero^{neg}ative or unknown; ^{neg}sero^{neg}ative at time of surgery, later became seropositive.

sex data and Lin *et al.* (2013) did not provide sex data for the included cohort. Powell *et al.* and Kelley *et al.* had male only cohorts.^{22,28} All studies reported on the HIV status of included patients, however the calculation method and reporting was inconsistent across the included studies. The interchangeable reporting of total patients and total joint procedures between the studies, as well as the unknown HIV status of a number of patients at the time of the procedure makes any comparison difficult.

Methodological quality of studies

The quality scores for the included studies ranged from 3 to 8 with a maximum score of 9. The median score was 5, with 8 studies considered to be of good quality *i.e.* score >5. A Newcastle Ottawa score of >5 was considered to represent a good quality study. The six most recent studies were considered to have a well-selected patient cohort.¹¹⁻¹⁶ The majority of studies scored poorly for cohort comparability as they failed to adjust for any major confounders in their analysis. No study stated independent blind assessment of outcome was used, therefore these studies may be susceptible to selection bias. The vast majority of studies used secure records *i.e.* medical records and operative notes to obtain outcome measures, however the definition of clinical outcome was variable between studies, making comparison difficult.

Outcomes of interest

Infection

All studies reported the infection rate post joint replacement, the results of which are summarized in Table 2. In total there were a combined 18,995 joint infections in 5,819,412 total joint replacements across the nineteen included studies. There was a higher percentage infection rate in the HIV positive cohorts compared to the HIV negative cohorts in thirteen of the studies.^{11,13-16,18,19,21-23,26-28} Four studies reported a higher percentage infection rate in the HIV negative cohort compared to the HIV positive cohort.^{3,17,24,25} The effect of each study is shown in the forest plot Figure 2. The study by Lubega *et al.* and Zhao *et al.* are excluded from the forest plot, as they reported no infections in either cohort.^{12,20} Mahure *et al.* and Lin *et al.* 2013 had a short in-hospital follow-up, therefore only early infections within this timeframe were included.^{11,14} The definition of infection differed or was not present across all included studies. As such, this lack of a standard definition for infection and the uncertainty regarding HIV status at time of surgery in some studies may affect the applicability and accuracy of the results.

All-cause revision

Seventeen studies reported the total

number of joint replacements that underwent revision for any cause.^{3,12,13,15-28} The results are summarized in Table 2. In total there were 117 revisions in 1506 total joint replacements. Ten studies reported on all-cause revision by HIV status.^{3,12,13,15-18,22,24,27} Nine studies did not provide adequate information regarding all-cause revision by HIV status and were therefore not included in the analysis.^{11,14,19-21,23,25,26,28} Zhao *et al.* did not have any revisions in either cohort and was therefore excluded from the forest plot.¹² The effect of each study can be seen in the forest plot Figure 3. There was a higher percentage all-cause revision rate in the HIV positive cohort as compared to the HIV negative cohort in five of the included studies.^{13,15,16,18,27} Four studies reported a higher percentage all-cause revision rate in the HIV negative cohort as compared to the HIV positive cohort.^{3,17,22,24} Overall, there was a wide variation in the reporting of the revision rate across the included studies and as such the results obtained have to be interpreted with caution.

A subgroup analysis of studies using non-haemophilic patient cohorts was performed for the primary outcome infection and the secondary outcome all-cause revision. Six studies stated using non-haemophilic cohorts.^{12,13,15-17,20} Zhao *et al.* had no incidents of infection or revision in either group and was therefore excluded from sub analysis.¹² Four studies were carried out

Table 2. Summary of reported infection and revision rates of included studies.

Authors & Year	Total infection (%)	HIV+ infection (%)	HIV- infection (%)	Total revision (%)	HIV+ revision (%)	HIV- revision (%)
Mahure <i>et al.</i> 2017 (11)	0.14	0.36	0.14	N/A	N/A	N/A
Zhao <i>et al.</i> 2015 (12)	0	0	0	0	0	0
Lin <i>et al.</i> 2014 (13)	12.5	9.1	5.58	5.58	9.1	5.38
Lin <i>et al.</i> 2013 (14)	0.33**	0.6**	0.33**	N/A	N/A	N/A
Issa <i>et al.</i> 2013 (15)	2.46	4.55	1.28	4.1	6.82	2.56
Capogna <i>et al.</i> 2013 (16)	1.93	4.4	0.72	2.42	5.8	0.72
Tornero <i>et al.</i> 2012 (17)	3.7	0	5.56	1.85	0	2.78
Rodriguez-Merchan <i>et al.</i> 2011 (18)	6.98	9.52	4.55	6.98	9.52	4.55
Goddard <i>et al.</i> 2010 (19)	1.43	5.88	0	10	-	-
Lubega <i>et al.</i> 2009 (20)	0	0	0	2.74	-	-
Solimeno <i>et al.</i> 2009 (21)	7.76	9.09	7.23	13.79	-	-
Powell <i>et al.</i> 2005 (22)	9.8	10	9.52	7.84	6.67	9.52
Silva <i>et al.</i> 2005 (23)	15.56	16.67 [#]	13.33	13.33	-	-
Norian <i>et al.</i> 2002 (24)	13.2	10	25	18.87*	20*	25*
Lehman <i>et al.</i> 2001 (3)	19.51	18.18	25	21.95	21.21	25
Thomason <i>et al.</i> 1999 (25)	17.39°	10.53°	50***	8.7	-	-
Vastel <i>et al.</i> 1999 (26)	20.69	31.25	7.69	17.24	-	-
Lofqvist <i>et al.</i> 1996 (27)	15.38	50 [#]	0	30.77	75	11.11
Kelley <i>et al.</i> 1995 (28)	8.82	18.75°	0 ser/ukn°	29.41	-	-

°Reported as patients; N/A, Not applicable; -Not stated; ser/unkn seronegative or unknown; [#]Assumed seropositive at time of surgery; *Defined as "failure"; **In-hospital follow-up only; ***Assumed seronegative.

over a similar time period, post introduction of HAART, had less heterogeneity and were considered to be of sufficient quality to pool the results and perform a subgroup analysis.^{13,15-17} The forest plot shown in Figure 4, demonstrates the risk ratio (RR) of infection between the HIV positive and HIV negative cohorts. In total the RR was 3.31, which favoured an increased risk for infection in HIV positive cohort. The forest plot shown in Figure 5, demonstrates the RR of all-cause revision between the HIV positive and HIV negative cohorts. In total the RR was 2.35 in favour of increased incidence of all-cause revision in HIV positive patients.

Discussion

This systematic review evaluated the totality of evidence relating to the outcome of total hip and knee arthroplasty in HIV-infected patients. The principal findings are that the overall quality of the studies in this area is poor and that infection and revision appear to be more likely in HIV-infected patients. Subgroup analysis of a small number of non-haemophilic studies, demonstrate an increased risk of infection and revision in HIV-infected patients. There was significant methodological and clinical heterogeneity amongst the included cohort studies assessing the outcome of hip and knee arthroplasty in HIV-infected patients. The methodological quality scores, as assessed by the Newcastle-Ottawa scale were variable. The quality scores of the cohort studies ranged from 3-8, with a median of 5. Eleven of the nineteen included studies achieved a quality score of 5 or less. A score greater than 5 is considered to be of good quality. The quality of studies

appears to improve over time. It can be inferred that the majority of included studies assessing the outcome of total hip and knee arthroplasty in HIV-infected patients are of poor quality.

Twelve studies included patients with haemophilia within the cohorts, with eleven studies designed specifically to assess out-

come of hip or knee arthroplasty in haemophilic patients, with varying degrees of sub-analysis for HIV status. The majority of these patients were infected with HIV by infected blood products during treatment for haemophilia. This often led to incomplete outcome reporting based on HIV status in a number of these studies, making accurate

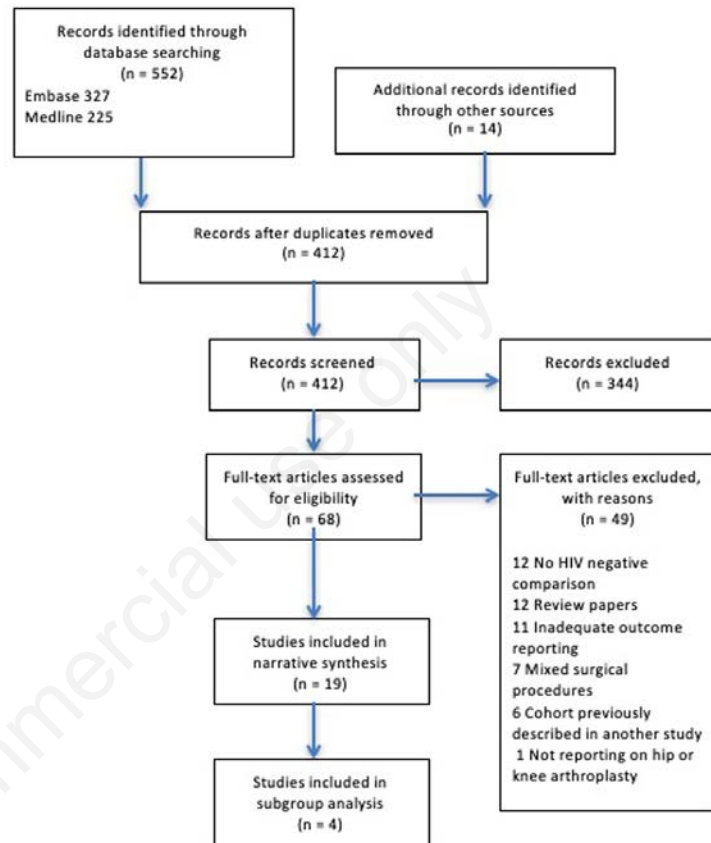


Figure 1. Flow diagram of study selection.

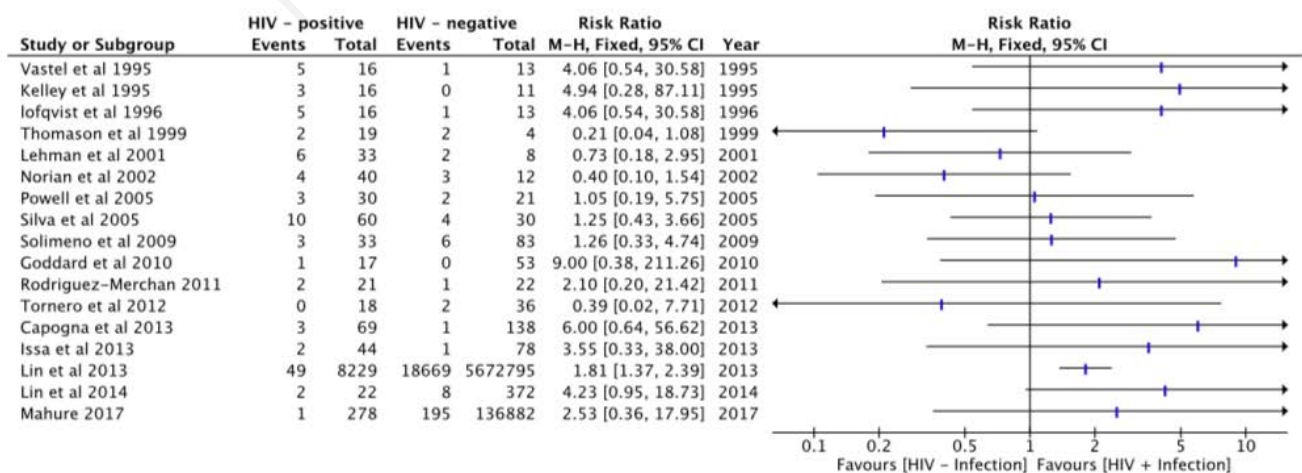


Figure 2. Infection rate.

analysis difficult. Similarly, as the primary goal of this systematic review is to assess the outcome specifically based on HIV status, the presence of a significant number of haemophilic patients (a group known to have worse outcomes for total joint arthroplasty) in the included studies is a major confounder. Overall there was an extremely heterogeneous group of patients in the included studies, with differing follow up periods and assessment methods, that limited the ability to pool data for analysis.

Assessing the primary outcome, wound

infection, thirteen studies favoured HIV-negative cohorts having a lower incidence of wound infection, while four studies favoured HIV positive cohorts having a lower incidence of wound infection. Assessing the secondary outcome revision, five studies favoured the HIV-positive cohort for increased incidence of all cause revision, while four studies favoured the HIV-negative cohort for all-cause revision.

These findings should be interpreted with caution. The methodological and clinical heterogeneity inherent in the included

studies meant that the results of each individual study could not be pooled for statistical analysis. Eleven of the included studies were considered to be methodologically poor. The confidence intervals for the risk ratios calculated across all the included studies for infection and all-cause revision were wide. In particular the study period ranged from 1972 to 2014. The evolution of HIV and our understanding of its pathophysiology and treatment have changed dramatically over this period. AIDS has progressed from a near universally fatal disease

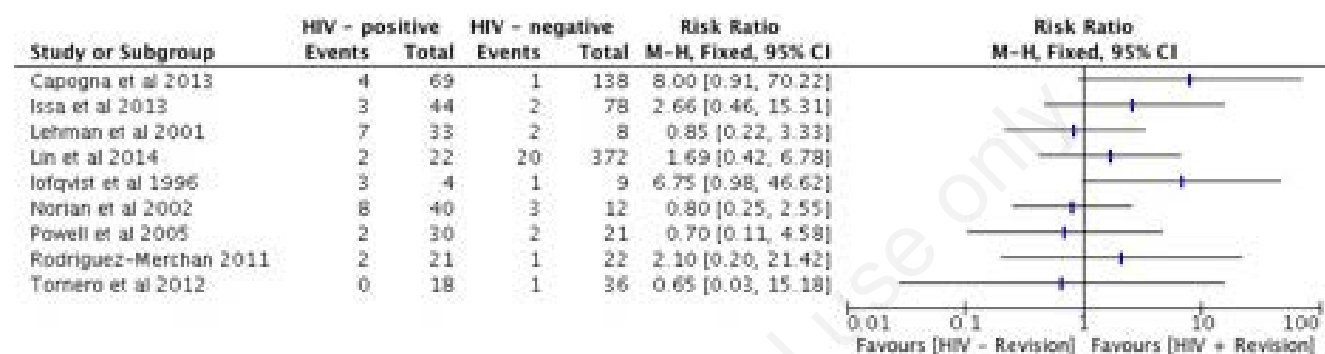


Figure 3. All-cause revision.

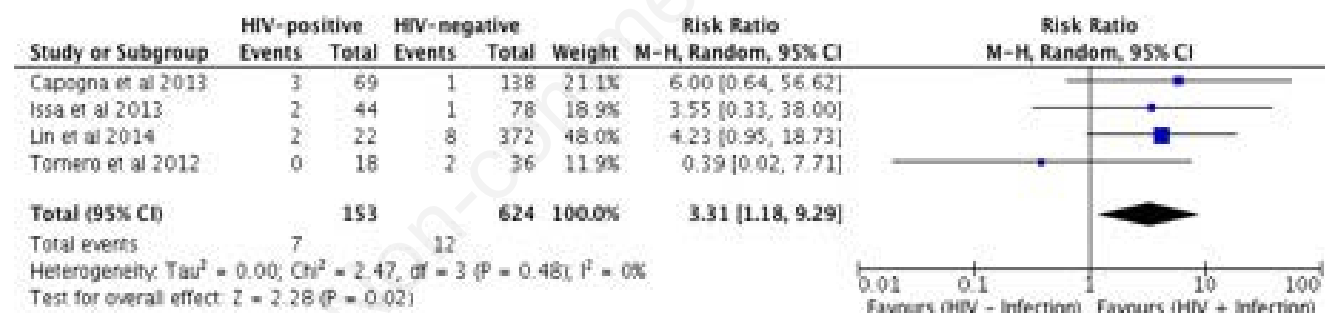


Figure 4. Subgroup Meta-analysis Forest plot of incidence of infection.

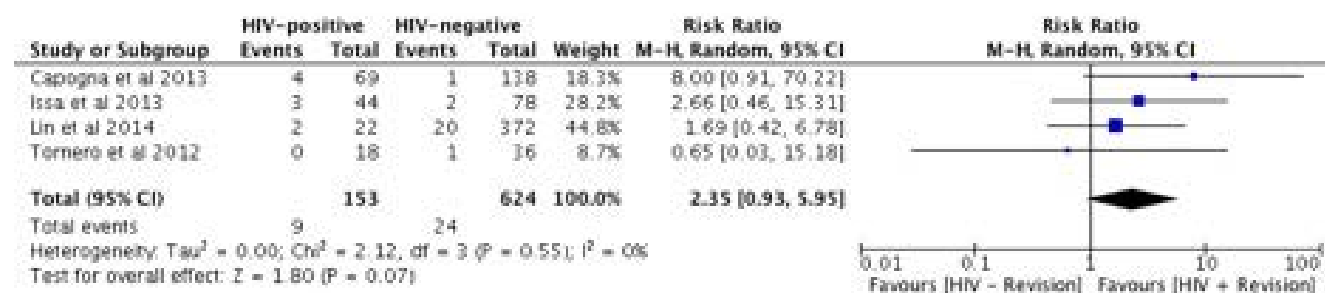


Figure 5. Subgroup Meta-analysis Forest plot of all-cause revision.

upon discovery in 1981 to patients having a life expectancy approximating the non-infected population today.⁽²⁾ The availability of effective treatment (HAART) varied considerably amongst the studies and this in itself is a confounding factor in relation to infection. Similarly, there has been improvements in operative technique and implant technology over time and this must be considered when interpreting the results of the outcome of infection and in particular revision. Antibiotic prophylaxis was variable amongst all included studies, again introducing a potential bias. The definition of infection varied or was not mentioned in the included studies, as such our definition of infection in this study included all reporting of infection from each study. Ideally, a modern consensus definition of infection, such as the 2018 musculoskeletal infection society (MSIS) definition could be used to provide consistency across the studies in terms of reporting.²⁹ This made any accurate pooling of the primary outcome using all the included studies impossible. Four studies performed using non-haemophilic cohorts and performed post introduction of HAART treatment employed similar methodology and were of good quality. For these reasons, it was possible to pool the results of these four studies and perform a subgroup analysis.

The study assessed outcome using a variety of measures including infection and revision. The search strategy was extensive to ensure all potentially relevant papers were identified and reviewed. No study was excluded based on language and this further strengthened the representation of all literature in our search. The methodological quality of each included study was independently assessed by two reviewers, using a validated scoring system and this further reinforces the validity of the assessment. The study has been written according to the MOOSE reporting guidelines for observational studies. This insures the format of execution of the systematic review is transparent for all to evaluate. The aim of the reporting guidelines is to improve the usefulness of systematic reviews and meta-analysis "...for authors, reviewers, editors, readers, and decision makers".⁷

Enayatollahi *et al.* performed a systematic review of HIV and total joint arthroplasty.³⁰ They found a lower incidence of infection in isolated HIV patients, compared with patients with HIV and coexisting hemophilia. However, they did not include a HIV negative control in the analysis. Dimitriou *et al.* also performed a systematic review and excluded hemophilic patients.³¹ The main outcome measure was complications, however included studies with and

without a HIV negative control cohort.

Overall, the study is limited by the quality of the studies that were available in the literature. The design of a significant majority of the included studies, particularly those dealing with haemophilic cohorts were suboptimal to answer the question of outcome in HIV-infected patients. There was also significant heterogeneity between the studies, with the study period spanning four decades. This was such that pooling of the results of all studies and performing statistical analysis was not possible, as it could lead to inaccurate and misleading conclusions. However, it was possible to pool data from four studies that were performed in the modern era, were of good quality and had similar methodology and perform a subgroup analysis. There was a relatively small number of outcome events reported in the studies overall, therefore analysis of hip and knee arthroplasty was carried out together and interpretation of results must take this into consideration.

Conclusions

This systematic review demonstrates an increased risk of infection and revision in HIV infected patients undergoing total hip and knee arthroplasty in a subgroup analysis. However, these findings are based on poor quality evidence in a limited number of studies and need to be interpreted with caution. Further research should concentrate on large, well-designed, prospective studies, that control for co-morbidities and employ standardised outcome measures to allow for direct comparison.

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