COMPARATIVE STUDY OF INTRAMEDULARY NAILING OF CLOSED FEMUR FRACTURES IN HIV POSITIVE AND NEGATIVE PATIENTS

By

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Supervisors' Declaration

As the candidate's supervisor I **have approved** this thesis for submission.

Signed: _____ Name: Prof T C Hardcastle Date: 25/09/2019

Student Declaration

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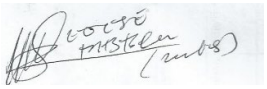

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Overview of the thesis

ABSTRACT/SHORT RESEARCH OVERVIEW (NOT EXCEEDING 350 WORDS)

Introduction

This study tested the hypothesis that there is no difference in both short-term infection rates and late implant sepsis and non-union rates between in HIV positive and HIV negative patients treated by reamed, closed femoral nailing for closed femur fractures.

Patients and Methods

Between February 2011 and December 2012 all patients with femur shaft fractures treated by reamed intramedullary nailing were recruited at a single referral hospital with a high rate of trauma and HIV prevalence. Thirty-two HIV positive patients and 80 HIV negative patients were enrolled and followed up clinically. Other variables included high or low energy injuries, age, AO/ASIF fracture pattern and CD4 counts. They were assessed for wound sepsis using the ASEPSIS method and followed up radiologically to assess for union of their nailed femurs. Follow-up was by telephonic interview to assess for late implant sepsis and non-union.

Results

There were no cases of early implant sepsis in either the 32 HIV positive or 80 HIV negative patients noted in the clinical and radiological follow up. Only one patient in the HIV positive cohort had a high ASEPSIS score, but this was deemed a superficial infection which resolved on antibiotics. A 3-year telephonic assessment of 32 HIV positive patients and 71 HIV negative patients with implants *in situ* and was undertaken. No cases of sepsis were found in the HIV group and one case of sepsis in the HIV positive group and this sepsis resolved after nail removal. Interestingly, this was in a patient who was initially HIV negative when nailed and later sero-converted. There were no cases of non-union in the HIV positive group or the HIV negative groups at 3 year follow up.

Conclusions

This research study found no increased risk of sepsis in closed femoral shaft fractures treated by internal fixation in HIV positive patients and adds to the limited literature regarding long term implant sepsis in HIV positive patients and concludes that there is no apparent increased risk of late, implant sepsis. There does not appear to be an increased non-union rate in HIV positive patients treated by reamed nailing fixation of closed femur fractures.

Contents

Part 1: The Review of Literature

RESEARCH QUESTION

Does HIV infection increase the risk of early or late implant sepsis and non-union rate in patients with closed femur fractures treated by closed reamed femoral nailing technique?

LITERATURE REVIEW

Introduction

Human immunodeficiency virus infection affects approximately 40 million people globally (1), with the majority of all infections (75.4%) in sub-Saharan Africa. In South Africa, KwaZulu-Natal (KZN) presented a unique challenge with the highest HIV infection rate of all the South African provinces (2, 3). KZN is a large province with geographical challenges, with many of the population living in rural regions (4). They have poor infrastructure, limited access to health and education and the many of the population survive on government grants. This fact firstly makes regular health follow-up difficult for post-operative patients and it is difficult for the rural patient to mobilise and rehabilitate, even with assistive devices. Trauma is prevalent in KZN and very high traffic loads locally and internationally increase the risk of major injury further. (5)

Basic science of bone healing

The skeleton is the basic support structure of all vertebrate animals. It is inherently one of the most important structures for mobility and functionality. When this framework has been disrupted by fracture, either low energy or high energy trauma, paracrine and autocrine intracellular pathways of healing are initiated to start the process of repair (6). Bone heals by two processes, primary or secondary bone healing. The primary bone healing involves the cutting cone technique and the secondary bone healing involves a more nutritionally demanding process with enchondral ossification (6). There are a lot of variables that affect this process of healing, importantly nutrition with albumin levels of < 3.5 g/100 ml thought to be poor prognostic factor for both bone and wound healing (6, 7). Although HIV was previously thought to be a risk factor of poor bone healing, Bates (8) did not find any significant risk in this population after clean surgery when compared with HIV negative patients. HIV positive patients may also be on multiple drug therapy and this increases the load on the hepatic system which assists in drug metabolism including synthesis and maintenance of the nutritional level of the body. Opportunistic co-infection, along

with other medical diseases (diabetes, hypertension and tuberculosis) can also complicate the bone healing process by increasing the nutritional demand of the patient. This result in low protein reserves and poor synthesis and response of both immune mediators and immune cells.

It is noted that different types of bone respond differently to the process of bone healing. There are other variables that also influence this process in orthopaedic surgery. The type of movement at the fracture site, the type of bone involved (6), surgical technique, type of fixation and other factors are contributory. This will make it difficult comparing different types of bones, with different quality of blood supply and different biomechanics, modes of implant fixation for rate of infection and healing process. Even the femur, for example, has different healing potential depending on which part is fractured. The proximal and distal ends have cancellous bone, compared to the shaft, and the two have different blood supply, muscle attachment and healing potential. If one bone in a single patient has different healing potential in different areas, this poses a huge challenge for the researcher trying to compare different bones in different patients because you may not even get the same results in the same patient. This is a challenge which was and still is difficult to resolve in orthopaedic surgery and many more studies to this effect have to be performed to better understand this process. This will help us to be pro-active rather than reactive in the management of both complex and simple fractures.

Many more variables have been cited as significant risk factors to non-union and/or sepsis after fractures. These include alcohol, NSAID, corticosteroids anaemia (6), poor nutrition (6,7); and also smoking (9,10). Many patients in sub-Saharan Africa are from rural poverty-stricken settlements, and this means that food security is an additional challenge for fracture healing (9). There may also be a lack of running water and proper sanitary facilities. In this type of environment, it becomes a challenge to maintain proper hygiene and infection, especially with bone-implants, becomes a significant health risk. (11)

HIV & AIDS

Human immunodeficiency virus (HIV) is a reverse transcriptase virus that attacks the immune system causing reduction in the CD4+ T cells and chronic inflammatory response (12). Sub-Saharan Africa has the greatest HIV prevalence and death rates compared to the rest of the world (13, 14). In South Africa, KZN was reported to have the highest number of people living with HIV, compared to the rest of the country (15). The prevalence of HIV in this part of South Africa has been estimated to be around 30% (3, 14, 16). Since 1994, health education in schools has increased with specific awareness increased in the field of teenage pregnancy and sexually transmitted infection, especially HIV. This has seen a steady behavioural

change among the youth and young adults, but there is still more to be done. Notable gains have been made in the fight against HIV with a decrease in the total death rate (14). These declines can also be partly due to the increase in the roll-out of anti-retroviral medication by government and people's awareness through the government run programmes in both schools and communities. Only patients with CD4+ count of <350cells/ul previously had access to government issued anti-retroviral treatment, due to the government policy at the time that the current study was done. This policy enabled access to anti-retroviral therapy before reaching AIDS defining stage of CD4+ cells of <200cells/ul. There is currently a recently introduced test and treat policy in place fully supported by the government that ensures that all persons living with HIV receive treatment, irrespective of CD4+ cell-count. This is the standard-of-care in other first world countries and it sustains HIV patients longer in a disease-free physiological condition, before presenting with AIDS defining conditions. The point of entry voluntary counselling and testing is actively practiced throughout KZN. The risk of opportunistic infection increases greatly if patients are in an AIDS defining stage, classified by the WHO as CD4+ cell count of <200cells/ul or AIDS defining pathologies.

HIV infection still carries a stigma in South Africa in general. There are low literacy rates, especially in the rural areas where the majority of the population are still more reliant on traditional medication. Health care workers do not have any particular influence in convincing the patient population to test, thus the state hospital gateway clinics have a policy to counsel and voluntarily test every patient entering the health care facility regardless of the illness. Subsequently there is no undue pressure on the patient to test and/or uncertainty on whether they will receive treatment if they refuse to test.

HIV and Orthopaedic Surgery

The unknown HIV status in many of our population raises a particular concern of probable increased risk of both infection and non-union of fractures after implant surgery. Also, known HIV positive status raises concerns that patient may receive sub-standard operative treatment because of fear of increased risk of infection by the treating surgeon. Earlier studies have supported this hypothesis (17, 18) but the more recent literature has found no significant increase in risk of implant sepsis and non-union in HIV positive patients when compared with HIV negative patients (16, 18-21). These studies compared different bones, with multiple operations and different patients. The challenge of different healing potential, operative procedures and biomechanics of both implants and bone were not accounted for.

Locked Femoral nailing

The locked femoral nailing technique was developed to improve the outcome of morbidity in femoral fractures. In earlier years, femoral fractures were treated by skin traction and plaster of Paris bracing which gave very poor results, i.e. malunions and stiff knee (22). The treatment of femoral fractures evolved to plate fixation, which in itself, came with more challenges. Sepsis, non-union and mechanical failure were some of the more pressing concerns for the orthopaedic surgeon. During the era of Closed Küntscher nailing, non-union and infection rate were reduced and function improved. This nailing technique did not control rotation and shortening. With the evolving modern transport systems, increasing access to automotive vehicles by an increasingly younger population and, more commonly in the local environment, high alcohol consumption, high energy injury is becoming more frequent (5). Locked femoral nailing techniques are an absolute necessity for early mobilisation, better rehab and early return to work. Locked femoral nailing is the standard of care technique for femoral shaft fracture fixation in most local units (5). It is a less invasive technique with minimal soft tissue disturbance around the fracture site, maintains the length of the patient's femur and adequately controls the rotation in the axial plane.

Harrison (17) compared different bones with different healing capabilities, while Howard, Aird and Phaff (16) and Seron and Rasool (23) compared open fractures which have higher risk of infection due to contamination as compared to closed fractures. This is a very serious and concerning variable that cannot be ignored. There is no current study comparing non-union and implant sepsis in a single type of bone in closed fractures of HIV positive patients.

The reaming technique has gained popularity in literature and has proven to increase the rate of fracture union in femur fractures (24). This technique is the local standard in all femur fractures treated with intramedullary nails. It is challenging to classify and adequately explain and interpret the complexity of fractures in long bones. This type of communication between professionals had to be standardised through classification systems. In literature it has also been proven that the AO classification is prognostic of outcome of closed femur fractures (25). The closed reamed femoral nailing technique gives a more predictive prognostic outcome of fracture healing in closed femoral fracture and minimises the variables of risk factors to non-union. This classification, though acceptable, like other classifications, still falls short of completely guiding the surgeon in all aspects of surgical intervention.

Timing of operative fixation

In high-income countries, the standard of care is to offer surgical intervention to trauma patients as soon as possible after stabilisation at a health facility, or on the next available slate. This reduces the complications of trauma, enables rapid rehabilitation and return to work or functionality. This makes sense if the transport of the patient to the appropriate facility of care is suitably quick, the facility is well staffed and has primary equipment, theatre time and more importantly, skilled labour to perform the work at hand. This is a challenge in KZN (5). These challenges may result with presentation of trauma as long as five days after the actual incident and sometimes, longer. This results in fractures that are difficult to reduce because of the development of callus in a non-anatomical mal-aligned position. As a result, closed fractures may need to be converted to open reduction techniques in order to mobilise the sticky callus bone formation, thus reduce the fracture and allow locked femoral nailing. There is also a risk of the operation lasting longer and resulting in increased risk of sepsis and septic non-union (26).

The level of surgeon experience is also very important to consider. The more experienced surgeon is more likely to take much less time operating than a junior doctor. But, on the other hand, a more experienced surgeon is more likely to operate on more complex and challenging fractures than a junior surgeon. This factor may result in senior surgeons taking more time to perform a femoral nailing. The complexity of the fracture should be taken into account and graded to be able to measure this variable. The AO classification system has proven to be prognostic of femoral non-union while taking into account the complexity of the femoral fracture (25). This classification provides an idea of the amount of energy transferred to the fractured femur, the amount of periosteal contusion or disruption and the stability of the fracture site. These factors are very important to the clinical outcome of the operation and the patient's morbidity i.e. malunion, shortening, progression angle and return to pre-morbid activity.

Other variables

There are other noted variables that contributes to implant sepsis and non-union. Smoking is a well-documented factor causing non-union in fractured bones (9,11). Cigarettes have a lot of carcinogenic chemicals including nicotine. Nicotine has an effect in inhibiting the process of neovascularization which is pivotal in fracture union early in the process of fracture healing. This aspect is part of lifestyle behaviour that can, though difficult, be modified or stopped entirely to improve the patient's health in general.

In 2011 Aird and co-workers (16,19,20) published their results of the effects of HIV on early wound healing in open fractures treated with internal and external fixation. The study was conducted between May 2008

and March 2009 at Ngwelezana hospital. The results of this study suggested that HIV is not a contraindication to internal or external fixation of open fractures, and HIV is not a significant risk factor for acute wound or implant infection. This study by Aird and co-workers' work will act as a pilot to help understand the complexity of this complication of non-union and implant sepsis in HIV positive patients when compared to the HIV negative patients treated with locked femoral nailing in closed femur fractures.

Conclusion

Fractures are complex and the influence of HIV positivity on the outcome in terms of non-union and septic complications is not yet well-defined. This aspect requires further research.

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Part 2: A submission ready manuscript.

Abstract 271 words

Introduction

It is unknown if there is a difference in short-term, or late implant sepsis and non-union rates between HIV positive and HIV negative patients treated with reamed, closed femoral nailing for closed femur fractures.

Patients and Methods

Between February 2011 and December 2012 all patients from a single referral hospital with a high rate of trauma and HIV prevalence with closed femur fractures included: 32 HIV positive patients and 80 HIV negative patients. Injury severity, age, AO/ASIF fracture pattern and CD4 counts were assessed. Wound sepsis was assessed with the ASEPSIS method. Radiological assessment for union was done. Telephonic follow-up was undertaken for late implant sepsis and non-union.

Results

No cases of early implant sepsis in either the 32 HIV positive or 80 HIV negative patients were noted at follow-up. One patient in the HIV positive cohort had a high ASEPSIS score, deemed a superficial infection which resolved on antibiotics. A 3-year telephonic assessment of 32 HIV positive patients and 71 HIV negative patients with implants in situ and was undertaken. No sepsis was detected in the HIV(-) group and one case of sepsis in the HIV(+) group that resolved after nail removal in a patient who was initially HIV negative and later sero-converted. No cases of non-union in either group was noted at 3 year follow-up.

Conclusions

We found no increased risk of sepsis in closed internally fixated femoral shaft fractures HIV(+) patients and concludes that there is no apparent increased risk of late, implant sepsis. There does not appear to be an increased non-union rate in HIV positive patients treated by reamed nailing fixation of closed femur fractures.

Keywords:

HIV; Femur fracture; closed fracture; LMIC; implant infection; long-term follow-up

Comparative Study of Intramedullary Nailing of Closed Femur Fractures in HIV Positive and HIV Negative patients

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Comparative Study of Intramedullary Nailing of Closed Femur Fractures in HIV Positive and HIV Negative patients

Introduction

Human immunodeficiency affects 38.8 million people globally, with 1.2 million new HIV infections in 2015 and with 75.4% of all infections in sub-Saharan Africa in 2015 (1). There are 5 million people affected in South Africa with 18% in the adult population between aged between 15years and 49years of age infected.(1) A particularly high prevalence exists in the province of KwaZulu-Natal (KZN) which is the second most highly populated province in South Africa.(1) This area also has a high trauma rate due to a multiplicity of causes such as interpersonal violence, gunshot wounds and high energy injuries caused by motor vehicle collision (MVC) with a large proportion of these being pedestrian vehicle collision (PVC). Recent statistics rank South Africa 42nd highest in the world in the road mortality rate (WHO - 2013) (2, 3) with 31.9 deaths per 100 000 population of which 37% were PVAs.

There were initially major concerns about treating HIV positive patients with internal fixation because of fears regarding both early and late implant sepsis. Research from the 1990s and early 2000s (4-6) suggested very high rates of implant sepsis especially in open fractures and there was a tendency to manage some fractures that would normally have been internally fixed in HIV negative patients, by other means and avoid internal fixation. More recent literature has suggested that early implant infection rates in HIV positive patients are not significantly different from infection rates in HIV negative patients in closed fractures, arthroplasty and also in open fractures.(5, 7, 8) Also the concern over late implant sepsis in HIV positive patients is not supported in the paucity of the literature that has addressed this issue.(8, 9)

There has also been concern regarding delayed and non-union of fractures in HIV positive patients. Harrison (10) reported delay in times to union in open tibial fractures treated initially by external fixation and then converted to plaster, though other studies have not shown statistical differences in union times in HIV positive cases compared to HIV negative cases (11).

We performed a retrospective, observational, comparative study of prospective cohorts of HIV negative and HIV positive patients, treated by interlocking nailing of closed femur shaft fractures in a single institution with a high trauma load and high HIV positive prevalence. We compared early infection rates and non-union rates and also did a long term follow up looking specifically at late infection rates and non-union rates in both cohorts of patients. Almost three million people live in the area of northern KwaZulu-

Natal in South Africa and are referred to a single trauma centre from 14 district hospitals (12). There is a local, catchment population of 334,459 people in the area served directly by the trauma centre (12).

Patients and Methods

Over a 23-month period from February 2011 to December 2012, all adult patients with femur fractures admitted to the trauma unit were recruited for the study. Inclusion criteria were patients 16 years or older with closed femur shaft fractures that were treated by a standard, reamed 10 mm interlocking nail with post-operative clinical and radiological follow up for 6 months or more and long-term telephone follow up of 3 years or more. Proximal femur fractures that required fixation with a more complex type of nail, with proximal fixation along the neck of femur, were not included in the study. Further exclusion criteria were femur fractures initially treated with external fixation and later converted to an interlocking nail, femur fractures that were plated, open fractures including GSW fractures and patients who could not be followed up adequately. Patients with an unknown HIV status and refusal to be tested were also excluded. Additionally, polytrauma cases with other injuries that might cause an increased risk of sepsis in the nailed femur, such as open fractures in the same limb or a laparotomy for bowel injury, were excluded.

Patients were routinely encouraged to be HIV tested and counselled as part of the protocol for inpatients in the hospital. Testing and counselling were done by Health Care workers (HCWs) not involved in the study. Patients already on ARV treatment had their treatment continued whilst in hospital and in keeping with the national protocol regarding the CD4 count in 2011 and 2012, (13) patients with CD4 counts below 350 cell/ul or patients with signs of clinical AIDS, were started on treatment, usually after their discharge from hospital. The national protocol of commencing ARV therapy to all HIV positive patients, irrespective of CD4 count, only commenced in 2016 (6). Twelve HIV positive patients were on ARV therapy at the time of their admission with CD4 counts ranging from 22 – 1551.53 cells/ul with a mean of 602.73

Ethical approval for the initial part of the study was obtained from the hospital ethics committee and later, approval for the longer follow up was obtained from the UKZN Biomedical Research Ethics Committee (BREC), BREC ref: BE354/14.

All patients were treated by closed, ante-grade intramedullary locking nails after reaming with Smith and Nephew 10mm diameter Trigen nails (Smith and Nephew, Memphis, Tennessee). Operations were

scheduled for routine trauma lists and were done within a few days of admission to the trauma centre. Delays in operations from the time of injury were generally because of delays in transferring patients from district hospitals to the trauma centre. Operations were performed by specialists and medical officers, either experienced or under supervision.

A number of clinical parameters were recorded including alcohol intake, smoking, AO/ASIF classification of the fracture, operating time (measured from incision to closure of the wound), level of expertise of operating surgeon, New Injury Severity Score (NISS), number of operations performed on the patient for additional injuries and categorization of the fracture as high or low energy. The AO/ASIF fracture classification was done by one investigator (MK) reviewing all X-rays on Picture Archiving and Communicating System (PACS; Agfa HealthCare, Mortsel, Belgium).

Initial follow up was done by one investigator (M.P.) in the routine fracture clinics with clinical assessment and X-rays taken at 4 weeks after discharge with further follow up and X-rays taken between 2 – 12 months post operatively until clinical and radiological union was established. Clinical union was regarded as the ability to walk unaided with no discomfort and radiological union was regarded as bridging callus seen on 3 or more cortices on A-P and lateral X-rays.(8, 14) Surgical wounds were assessed for signs of infection using the ASEPSIS score.(15) The ASEPSIS score has been used by this unit and others in previous publications.(8, 9) For the long term follow up, a telephone-based follow up questionnaire (Fig. 1 – telephonic ques) was then performed by one investigator (MK) at least 3 years after the initial operation. A similar questionnaire has been used previously in this unit in a study by Phaff and co-workers (8) and was a combination of some aspects of the ASEPSIS score as used by Bates (5, 9) and **non-union criteria as used by Hernigou and Frederic (14) and was directed at assessing late implant sepsis and non-union**.

Figure 1. Telephonic questionnaire.

Pain from injury at present	No pain	Little pain	A lot of pain
Pain wakes me up at night	Yes/no		
Walking aid (For lower limb injuries)	None	1 x crutch	2 x crutches
	Walking frame	Wheelchair	Bedridden
Can use arm to dress (for upper limb)	Yes/no		
Are the joints involved stiff?	Yes/no		

Wounds on the affected limb	No wounds	Small wound <2cm	
	Big wounds >2cm	Many wounds >1	
Discharge from wounds	Yes/no		
RVD status	Positive	Negative	Unknown
Last CD4 count			
Date Last CD4 count			
On ARVs	Yes/no		
When started on ARVs			
Metal removed	Yes/no		

Statistical analysis

The data collected was represented as categorical data and collected into a database compiled in Microsoft Excel (Microsoft, Redmund, WA) where further graphical representation of the data was also generated. The statistical analysis was performed with PAST version 3.24 (O Hammer, Oslo, Norway) and within each sub-category significance testing was performed with Chi-squared test with a significance level set at $p < 0,05$. A multivariate analysis was done to establish the association of each of the variable with our outcome (non-union and implant sepsis) using Chi-Squared p-value and Mann-Whitney U. A significant difference was considered if any of the variables has a p-value of $p < 0.05$.

Results

A total of 147 patients with femur fractures were initially recruited into the study but 35 patients were excluded because of refusal to be HIV tested or inadequate follow up. This gave a total of 112 patients included in the initial part of the study. For the long term follow up, 7 patients were lost to follow-up and this gave a total of 105 patients in the longer follow up at 3 years or more. There were two patients in the study group who had bilateral femur fractures. One patient had a femur nailed with the opposite side plated. The second patient has both femurs nailed. Subsequently, at 3 months in the patient with bilateral nails, one nail broke at the distal screw hole and was revised to a locking plate and this nail breakage was regarded as a mechanical failure. These 2 patients were included in the study giving a total of 112 patients (with 113 femoral nails) in the initial part of the study and a total of 105 patients with 105 nailed femurs in the longer-term study. Fig.2 (flowchart)

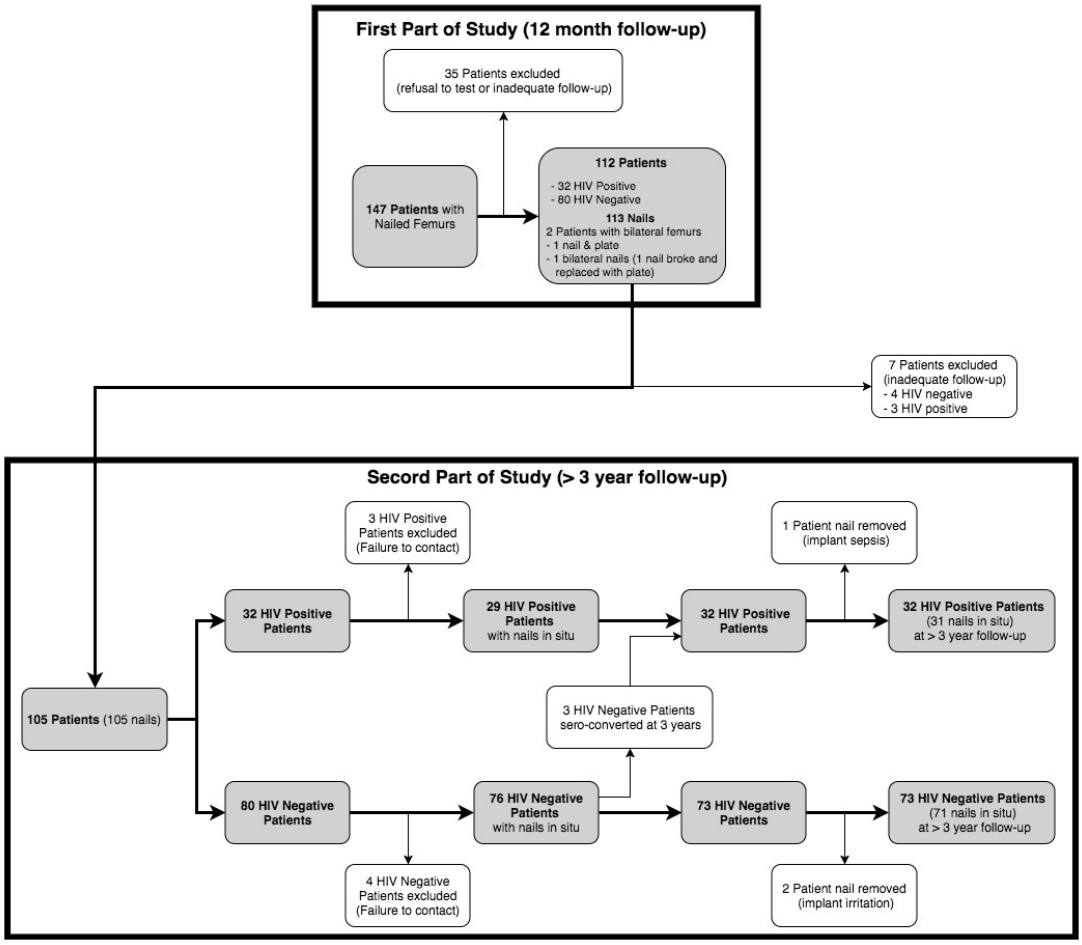

Fig. 2. Flowchart giving an overview of both the 1 year and more than 3 years follow-up

There was only one case of early wound sepsis in the HIV positive group and no cases of sepsis in the HIV negative group noted in the initial clinical assessment performed in the first 12 months post-operatively. The one HIV positive patient with sepsis had an ASEPSIS score of 26 at his 4 weeks follow up and a wound swab cultured Enterobacter. He was started on antibiotics with complete resolution of the sepsis when reviewed four weeks later and there was no suggestion of sepsis at the 3 year follow up. This high ASEPSIS score was therefore assumed to be a superficial soft tissue infection and not an implant sepsis. There was therefore no implant sepsis in either the HIV positive or HIV negative groups during the first part of the study, concluding at 1 year.

All fractures in the HIV positive group had united by 6 months and all but two (2,5%) in the HIV negative group had united at 12 months. Of these 2 failures in the HIV negative group, one was in a patient with a broken nail that was revised to a locking plate at 3 months, which subsequently united and the second failure was a non-union that was revised to a plate at 9 months post-operatively and united after plating. Risk factors such as smoking (14), alcohol intake and poverty (risk factors for poor lifestyle and nutrition (16, 17), were recorded, but were not related to non-union or implant failure.

Overall, 77 of the totals of 112 patients (68.8%) were classified as high energy injuries mainly caused by motor vehicle collisions (MVC) 58 patients (p-value: 0,283) and pedestrian vehicle collisions (PVC) 19 patients (p-value: 0,036). Forty-nine of the 80 HIV negative patients (61.25%) sustained high energy fractures compared to 28 of 32 HIV positive patients (87.5%). The AO/ASIF classification of the femur fractures for the HIV positive and HIV negative groups is shown in (Fig. 3 – AO) B2 and B3 fractures predominated in the HIV positive group with there being eight (25%) B2 fractures (bending wedge) and eight (25%) B3 fractures (comminuted wedge) in this group of 32 patients. (Fig. 4- NISS) In the HIV negative group, A type fractures predominated, with 44 of the 80 fractures (55%) being A1 (7.5%), A2 (16.25% & p-value: 0,07) or A3 (31.25% & p-value: 0,008). The majority of patients, 85 of 112 (75.9%) had a NISS of 9 (p-value: 0,0002), indicating only an isolated femur fracture. The median NISS was 9 in both HIV negative and HIV positive patients. The HIV positive group had a mean age of 35 years compared to a mean age of 31.6 in the HIV negative group. Eighteen of the 32 HIV positive patients were aged 30 – 39 years (56%) compared to only 12 of the 80 HIV negative group in their 30s (15%). There were 16 males and 16 females (50%) in the HIV positive group and 59 males and 21 females (26.25%) the HIV negative group.

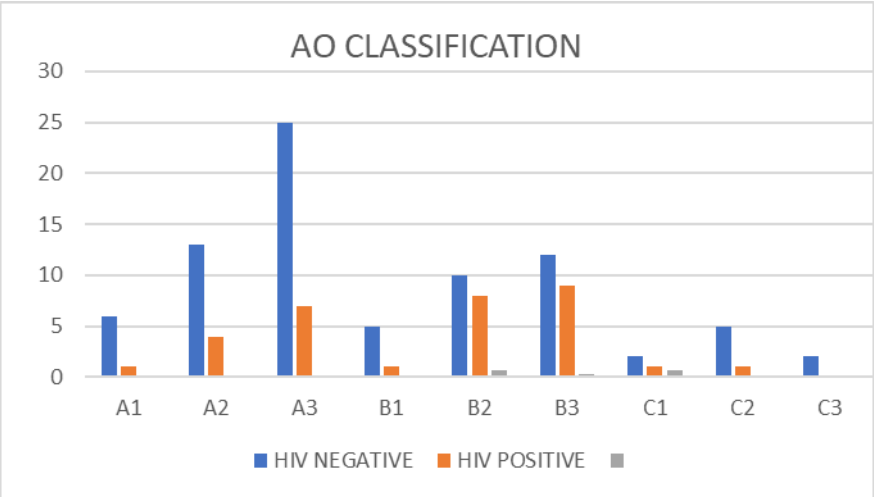

Fig. 3. AO classification of femur fractures showing high percentage of Type-A fractures (44 of 80 fractures) in the HIV negative patients (55%) and high percentage of Type-B fractures in HIV positive patients (56%) with 8 (25%) B2 fractures (bending wedge) and 8 (25%) B3 fractures (comminuted wedge)

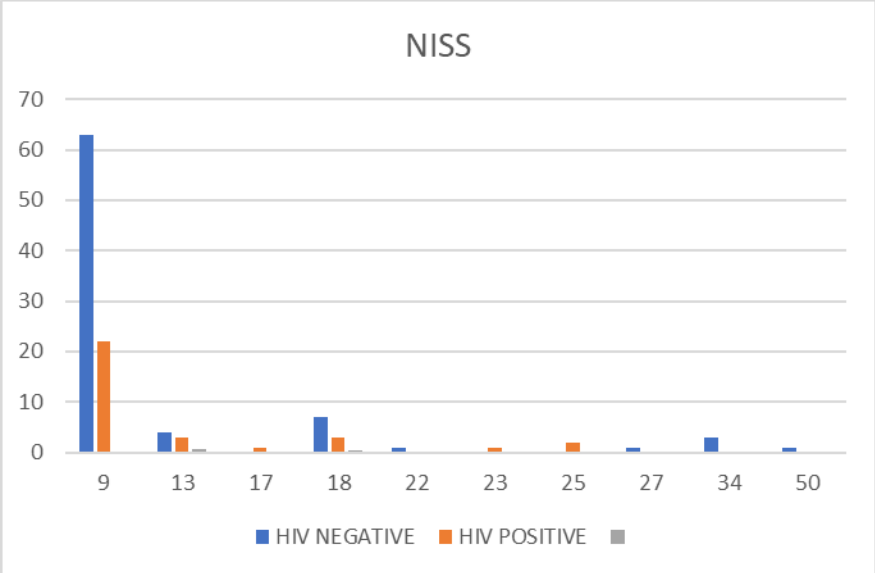

Fig. 4. NISS showing majority, 85 of 112 (75.9%) of patients (75.9%) with a low score of 9 indicating an isolated femur fracture.

There were 32 HIV positive patients in the study with CD4 counts available in 25, ranging from 22 – 1551.53 cells/ul with a mean of 602.73. Seven patients had CD4 counts <350 cell/ul. Eighty patients were HIV negative when they entered the study and of these, 3 patients later sero-converted and became HIV positive at the 3-year telephone follow up.

Operative time was less than 60 minutes for 42 of total of 112 patients (37.5% & p-value: 0,042), between 60 – 120 minutes in 66 of the cases (58.93% & p-value: 0,026) and more than 120 minutes in 10 patients (8.9% & p-value: 0,297). These prolonged operative times were recorded in patients requiring additional procedures after their femurs were nailed e.g. tibial nail, forearm fixation for multiple fractures. Eighty of the 112 patients were operated on by medical officers (71.4% & p-value: 0,0032) with consultants operating on 32 of the total (28.6% & p-value: 0,019) (Fig. 5).

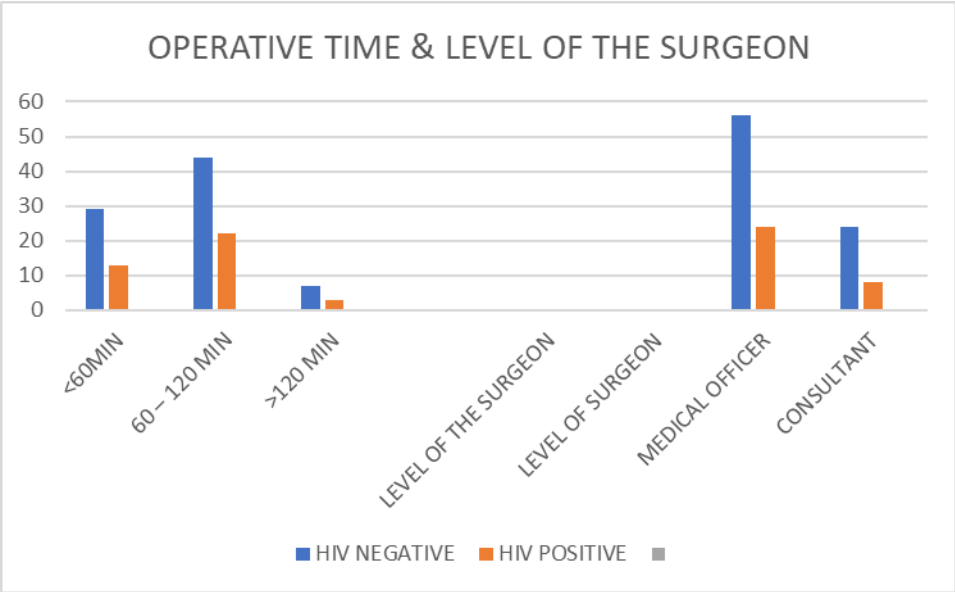

Fig. 5. Operative time was less than 60 minutes for 42 of total of 112 patients (37.5%), between 60 – 120 minutes in 66 of the cases (58.93%) and more than 120 minutes in 10 patients (8.9%). These prolonged operative times were recorded in patients requiring addition procedures after their femurs were nailed e.g. tibial nail, forearm fixation for multiple fractures. Eighty of the 112 patients were operated on by medical officers (71.4%) with consultants operating on 32 of the totals (28.6%)

At the 3-year follow-up, a total of 105 patients out of the original 112 were contacted and assessed with the telephonic questionnaire, specifically assessing late sepsis and non-union. Of the original cohort of 32 HIV positive patients, telephone contact was made with 29 and no patients were found at 3 year follow up to have any suggestion of late sepsis or non-union. Of the 80 patients in the original HIV negative group telephonic assessment was possible with 76 patients and there was one patient with suspected implant sepsis. This was a patient who was initially HIV negative at the time of femoral nail insertion and so was initially included in the HIV negative cohort. He later sero-converted and developed a sinus at the site of nail insertion and had the nail removed at 24 months post-operatively because of suspected implant sepsis, which resolved after nail removal, without antimicrobials. This patient was therefore included in the HIV positive cohort in the longer follow up. Two patients from the HIV negative group had their nails removed for mechanical irritation after 1 year and prior to their 3 year follow up. Their fractures had already united with no signs of sepsis when the nails were removed and although there was no sepsis noted at the 3 year follow up, they were not included in the numbers for the long term follow up of late

implant sepsis. Two further patients from the HIV negative cohort had sero-converted and were therefore included in the HIV positive group for late follow up but they were in the HIV negative cohort for assessment of early sepsis.

Discussion

The results of the current study support the hypotheses that that there is no association between HIV positivity and early and late implant sepsis and also no association between HIV positivity and non-union in closed femoral fractures treated by closed, reamed nailing. This study compared a relatively large cohort of HIV positive patients (32) with a larger cohort of HIV negative patients (80) treated at a single institution with a standardized operation and found low rates of infection in both cohorts with both short-term follow up and then longer term follow up at >3 years. These results are in keeping with other studies looking at wound infection and implant sepsis in HIV positive patients with closed fractures. An early prospective study from Malawi (18) comparing wound infection rates in 28 HIV positive patients and 108 HIV negative patients treated by internal fixation showed no statistical difference between the two groups. More recent studies by Bates in 2012 (5) also from Malawi, compared a large series of 118 HIV positive patients with 418 HIV negative patients and smaller series by Hao et al in 2015 (19) from Denver, USA confirm the findings of no increased risk of early implant sepsis in HIV positive patients.

Early studies by Piaiemont in 1994 (20) and Harrison in 2002 (18) raised concerns about sepsis risk with open fracture treatment and subsequent studies have produced differing results. Howard and co-workers (21) reported lower infection rates in a cohort of HIV positive patients with open tibial fractures treated by both internal and external fixation and Aird,(7) from the same research group, showed no statistical difference in early infection rates between HIV positive and HIV negative patients treated with internal and external fixation although Grade 1 open fractures with low CD4 counts did show a statistically significant increase in wound infection rates. A further paper from South Africa, by Nieuwouldt and co-workers (22) looking specifically at open grade III tibial fractures treated by a circular external fixator, showed very low sepsis rates in both HIV positive and negative patients (4.3%) and no difference in infection rates between the two groups.

There is a paucity of evidence regarding late implant sepsis in HIV positive patients. There is a concern that as HIV disease progresses and immunity falls, implant sepsis may increase as seems to happen with reactivation of old haematogenous osteomyelitis (23). Prospective studies from Malawi by Harrison (10)

and Graham (9) showed no late implant sepsis in patients with closed fractures with follow up for 12 months and 27 months respectively. Low rates of late implant sepsis in open fractures were also recorded by Graham (9) with no sepsis noted in 12 patients. Phaff and co-workers (8) recorded sepsis rates of 8% in both HIV positive and HIV negative patients with a follow up period of over 3 years in patients with open fractures and implants still in place. A different way of looking at chronic bone infection rates in HIV positive patients was explored by Kruger and co-workers (24) who retrospectively reviewed 303 patients referred to a tertiary unit with chronic bone infection, mostly without implants. They noted a similar rate of HIV positivity in their patients with chronic osteomyelitis (24.5%) as existed in the local adult population (21%), implying that HIV may not be a significant risk factor in chronic osteomyelitis.

Union of fractures is usually defined by a combination of clinical and radiographic criteria, the most commonly used being the absence of pain or tenderness at the fracture site and the presence of bridging callus at the fracture site (25). Radiological union is usually defined by bridging callus seen on three cortices on standard A-P and lateral views (14). Non-union rates in nailed femur fractures vary from 0% (26, 27) up to 5% and 7% respectively in series reported by Hammermacher (28) and Herscovici (29). These latter two papers however reported on unreamed nails and other studies comparing reamed and unreamed nails in femur fractures have confirmed higher non-union rates in unreamed as compared to reamed nailing techniques. A multicentre, randomized trial from the Canadian Orthopaedic Trauma Team (30) compared a series of 107 unreamed femur fractures treated with a smaller diameter nail with 121 fractures treated with a relatively larger diameter nail after reaming and noted a 7.5% non-union rate in the unreamed group compared to a 1.7% non-union rate in the reamed group.

Delayed and non-union of fractures in HIV positive patients with both open and closed fractures has been assessed in few papers, many of which do not give their methods of assessment or detail for determining delayed and non-union. Harrison 2004 (31) recorded 0% non-union in 26 HIV positive patients with closed fractures assessed both clinically and radiologically. Hau and co-workers (19) recorded no non-unions in their series of 24 closed fractures in HIV positive patients. Phaff (8) in his long term follow up of implants in HIV positive patients with open fractures, recorded 1 patient out of 13 HIV positive patients (7.5%) with non-union after external fixation of a tibial fracture. This was in a patient with a low CD4 count (105 cells/uL) who eventually united after conversion to a nail. Nieuwouldt and co-workers (22) in a retrospective review of 94 consecutive grade III open fractures treated definitively by circular frame fixation, recorded no non-unions in 31 HIV positive patients. Studies by Abalo and co-workers (32) and

Aird and co-workers (7), however recorded higher rates of non-union in open fractures at 11 % and 15% respectively, but many of the risk factors for non-union were not recorded in these papers. In our series, all the femur fractures were reamed and nailed with a relatively large nail (10 mm diameter) and our low non-union rates in both the HIV positive and negative groups (0% and 1.25% respectively) are comparable to those recorded in earlier studies. Tornetta (27) recorded no non unions in 89 reamed femurs and the Canadian Orthopaedic Trauma Society (30) recorded 2 non unions in their series of 121 reamed femurs.

In our series the HIV positive group had a higher percentage of high-energy injuries (87.5%) compared to the HIV negative group (61.25%) with only 4 out of 32 fractures being classified as low energy injury in the HIV positive group. Also, the HIV positive group had a high percentage of type B fractures (56.25%) compared to HIV negative group (33.75%), reflecting a more severe type of fracture pattern. These findings are surprising considering that HIV disease and ARV treatment are both thought to cause a decrease in bone density and osteoporosis (33) and the expectation would be that low-energy fractures would be more frequent in HIV positive patients compared to HIV negative patients. One consideration is that HIV positive patients may take more risks in their daily life especially when travelling, for instance, not using seat belts and travelling in the back of open vehicles.

The low median NISS score of 9 in this study is surprising considering the high rate of high energy injuries in both the HIV positive (87.5%) and HIV negative groups (61.25%) and with a total of 77 patients out of the 112 patients being involved in vehicle related trauma either as a car occupant or as pedestrian. This anomaly is explained by the large numbers of patients with femur fractures excluded from the study because of their associated injuries such as a laparotomy for a bowel injury or an associated open fracture in the same limb as the nailed femur fracture. These cases were excluded because these associated injuries could have resulted in an increased sepsis risk in the nailed femur fracture. In fact, the majority of patients in the study, 85 (75.9%), had a NISS score of 9, reflecting only a femur fracture as an isolated injury.

Human immunodeficiency virus (HIV) disease is associated with loss of CD4+ T cells, chronic immune activation and progressive immune dysfunction (33). There were seven HIV positive patients with CD4 counts <350cell/uL out of the total of 32 HIV positive patients followed up in the first part of the study. This figure of CD4 count of <350 cells/uL is noted because it has been regarded as signifying advanced HIV disease (7) and was also the level when ARV treatment was initiated according to the guidelines of South

African Dept of Health in 2010 (13) and these were the guidelines in place at the time of this study (7). None of these patients with low CD4 counts showed any evidence of the development of sepsis or non-union in the short term or longer follow up study. Most studies of HIV implant sepsis have very few recorded low CD4 counts and it is difficult to draw any conclusions regarding low CD4 counts and a possible increased risk of implant sepsis (7)

Long-term anti-retroviral (ARV) therapy, with certain treatment regimes, is now known to be a factor in the osteoporosis and fragility fractures seen in HIV patients on ARVs, but it is difficult to differentiate the effects of the drug treatment from the effects of HIV disease itself (33). ARV therapy, particularly therapy with tenofovir and ritonavir-boosted protease inhibitors (rPIs), reduces bone mineral density (BMD) (33) and predisposes to fragility fractures, increased bone turnover and possibly increases the risk of poor bone healing. In South Africa, with 7.1 million people living with AIDS in 2016 (1, 34) and nearly 4 million on ARV's, fractures rates associated with ARV therapy, can only be expected to increase.

There are a number of limitations to this study. The low risk of both infection and non-union in closed femur fractures treated by reamed intra-medullary nails means that the numbers in the study are not sufficiently powered to show statistical differences for both infection and non-union. The long-term follow up by telephone interview is not as rigorous an assessment as a clinical and radiological follow up. The intention with the telephone follow-up, was to call back patients with problems suggestive of sepsis or non-union and assess these patients both clinically and radiologically, but since there were no patients with problems, this more detailed follow up was not required in any patient. Although the initial clinical and radiological follow up was prospective, the assessment for infection using the ASEPSIS score was not blinded and so an element of bias and subjectivity could be present. Some of the strengths of this study are that the cohorts of patients are homogenous, all with closed femurs with no other risk factors for sepsis, with very standardized operations done in one centre. This study adds to our knowledge documenting long term follow up of HIV patients with implants.

In conclusion, this study again found no increased risk of sepsis in closed femur fractures treated by internal fixation in HIV positive patients, yet also adds to the paucity of literature regarding long-term implant sepsis in HIV positive patients and concludes that there is no apparent increased risk of implant sepsis. Also, there does not appear to be an increased non-union rate in HIV positive patients treated by reamed nailing of closed femur fractures.

Take home message

- There's very high prevalence of HIV/AIDS in the Sub-Saharan Africa with also very high trauma rates.
- This study confirms both in short-term and long-term follow-up, there is no statistical difference in infection rates between HIV positive and HIV negative patients treated with femoral nails in closed femur fractures.
- Seven of the 32 patients had low CD4+ counts (<350 cells/ul) and no clinical manifestation of AIDS. None of these patients had any sepsis or non-union. There is still however concern regarding implants sepsis in patients with clinical manifestation of AIDS and very low CD4+ count (<100 cell/ul)

Acknowledgement
Dr Alan Gould (statistics)

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Appendices

Appendix 1: The final Study Protocol (Include the final protocol which was given full approval by Brec and/or the postgrad office)

APPLICATION FOR EXPEDITED REVIEW

1. ADMINISTRATIVE DETAILS

NAME: PI - Prof/Dr/Mr/Mrs/Miss/Ms **NAME: Co-investigator**	Dr Mmakgabo Matthews Keetse Dr Martin Phaff
Professional Status (if student, year of study)	Medical Doctor, Orthopaedic Registrar 2nd year
Full time/Part time	Full Time
UKZN Department & Campus **(Full Address)**	UKZN Medical School
Hospital / Institution **(where employed, Full Address)**	King Edward VIII Hospital
Contact Telephone Numbers and email address	084 700 9745
HPCSA Number (or equivalent statutory health council registration no. as appropriate)	MP0662836
Title of Study:	Delayed implant sepsis and non-union in HIV positive with intramedullary nails for closed femur fractures

2. Will there be direct participant contact? **YES* / NO**

   If YES, please explain and attach Informed Consent and Information Sheets

   Telephonic follow up of participant to complete the study project

3. Where will the Research be carried out? (Hospital, clinic etc).

Hospital - Ngwelezana

4. Is this a retrospective study? **YES, It's a retrospective review of a prospective cohort**

   (a) Tick type of study: Other: Retrospective analysis of a prospective cohort study

5. Will participants' confidentiality be maintained? **YES**

   Explain: The participants are offered a specific number to their name that will be used in the review of their results to keep their name confidential

6. Will Informed Consent be obtained? **YES / NO**

   Explain:

   The study and its aim have been explained in the language of the patient and participation purely voluntary. The minimum admission age of our participants is 16yrs and patient below 18yrs we still need the parent to countersign for admission into the study

7. Is this project intended to produce any information of diagnostic significance to the patient? **YES**

   If yes, will such information be forwarded to the patient's physician?

   - In the event were the patient's implant turns septic the patient will be re-admitted and further definitive care will be instituted.

8. Proof of concept – justify scientific validity of project.

There is much reluctance in the use of implants in the HIV positive population and this create much difficulty and uneasiness when having to treat this population where the use of implants is definitively indicated and the use the of will maximize their treatment

9. Motivation for (justify) expedited review:

   Of the available studies, the have been a great challenge in the long term follow up of patient with implants especially in the trauma population. This creates a good understanding in the mid to long term follow-up of this patient and help evaluate if there is any differences between the HIV negative and positive population that supports

the fears already in existence in the surgical and medical fields and will help in decision making to optimize the treatment in the HIV positive population

10. I certify that all information provided above is correct and that it will apply throughout the performance of the proposed research and that I shall be responsible for the safeguarding of the confidentiality of human subject's information involved.

I agree to comply with the UKZN Biomedical Research Ethics Committee's Terms of reference and the SA Department of Health (2004) *Ethics in health research: Principles. Structures and processes,* and, if applicable, the SA Department of Health (2006) *South African good clinical practice guidelines.* All are available at http://research.ukzn.ac.za/ResearchEthics11415.aspx

Signature of Researcher: ORIGINAL SIGNED COPY SUBMITTED TO BREC

Names and signatures of supervisor(s), co-workers/co-investigators:

1) Mr Timothy Craig Hardcastle (Primary Supervisor)
2) Mr Paul Rollinson (co-supervisor)
3) Dr Martin Phaff (co-investigator)

Appendix 2: The Guidelines for Authorship for the Journal selected for submission of the manuscript

Guide for authors: Injury

Injury was founded in 1969 and is an International Journal dealing with all aspects of trauma care. Our primary aim is to facilitate the exchange of ideas, techniques and information between all members of the trauma team.

Topics covered include: trauma systems and management; surgical procedures, epidemiological studies, surgery (of all tissues) resuscitation; biomechanics, rehabilitation, anaesthesia; radiology, basic science of local and systemic response to trauma and tissue healing.

The Journal also publishes a series of scientific supplements, all of which undergo peer-review prior to publication.

The language of the journal is English (UK), for example, stabilisation, haematology, anaesthetic, centre, paediatric, mobilise.

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1. Standard Journal Articles (List all authors when six or less; when seven or more, list the first six and add et al. Do not repeat page numbers).

Frame JD, Frame JE. Modifying integra as a regeneration template in deep tissue planes. J Plast Reconstruct Aesthet Surg 2006;59: 460-4.

Books

1. Book chapter

Lister GD. Skin flaps. In Green DP, editor. Operative Hand Surgery. 3rd ed. New York: Churchill Livingstone; 1993, p. 1741-1823.

2. Book

Book: Mathes SJ, Nahai F. Reconstructive Surgery: principles, anatomy, and technique. New York: Churchill Livingstone; 1997.

Website

Uebersax J. A practical guide to local dependence in latent class models.

http://ourworld.compuserve.com/homepages/jsuebersax/condep.htm.

Dataset

[dataset] Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. http://dx.doi.org/10.17632/xwj98nb39r.1. Authors are strongly encouraged to check the accuracy of each reference against its original source.

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Appendix 3: Ethical approvals

Included hospital and provincial approvals as well as the BREC approval (or waiver if appropriate).

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12 March 2015

Dr Mmakgabo Keetse
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Dear Dr Keetse

PROTOCOL: Delayed implants sepsis and non-union in HIV positive patients with intramedullary nails for closed femur fractures: Degree Purposes (MMed). BREC REF: BE354/14.

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 14 July 2014.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 07 January 2015 to queries raised on 21 October 2014 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval.

This approval is valid for one year from 12 March 2015. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2004), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on 14 April 2015.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Professor J Tsoka-Gwegweni (Chair)
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Reference:
Enquiries: Dr O. C. Harbor
Date: 09 June 2008

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Prof Barker

Dear Doctors Aird, Rollinson and Grey

RE: YOUR APPLICATION FOR RESEARCH STUDY

We would like to acknowledge your application to the Ethics / Research Committee of Ngwelezane Hospital regarding your study looking at risk factors for wound and bone infections following internal and external fixation in open fractures in immunocompromised patients.

It was discussed at our meeting held on 13 May 2008 and we approve your application. You need to be aware that we are forwarding it to the Provincial Ethics Committee for their information.

Regards

.....
WENDY BARRETT (SECRETARY)

.....
DR O. C. HARBOR
ACTING CHIEF EXECUTIVE OFFICER

Appendix 4: Data collection tools

Figure 1. Telephonic questionnaire.

Pain from injury at present	No pain	Little pain	A lot of pain
Pain wakes me up at night	Yes/no		
Walking aid (For lower limb injuries)	None	1 x crutch	2 x crutch
	Walking frame	Wheelchair	Bedridden
Can use arm to dress (For upper limb)	Yes/no		
Are the joints involved stiff?	Yes/no		
Wounds on the affected limb	No wounds	Small wound < 2 cm	
	Big wounds > 2 cm	Many wounds > 1	
Discharge from wounds	Yes/no		
RVD status	Positive	Negative	Unknown
Last CD4 count			
Date last CD4 count			
On ARVs	Yes/no		
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Metal removed	Yes/no		