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Fracture healing in patients with human immunodeficiency virus in South Africa: a prospective cohort study

Running Head: **Fracture healing in patients with human immunodeficiency virus**

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Abstract

Background: Human immunodeficiency virus (HIV) reduces bone mineral density, mineralisation and turnover, and may impair fracture healing.

Setting: This prospective cohort study in South Africa investigated whether HIV infection was associated with impaired fracture healing following trauma.

Methods: All adults with acute tibia and femur fractures who underwent intermedullary nailing (IM) for fracture fixation between September 2017 and December 2018, at two tertiary hospitals, were followed for a minimum of 12 months post-operatively. The primary outcome was delayed bone union at 6 months (defined by the radiological union scoring system for the tibia [RUST] score <9), and the secondary outcome was non-union (defined as RUST

score <9) at 9 months. Multivariable logistic regression models were constructed to investigate associations between HIV status and impaired fracture healing.

Results: In total, 358 participants, who underwent 395 IM nailings, were enrolled in the study and followed up for 12 months. Seventy-one participants (71/358, 19·8%) were HIV positive (83 IM nailings [83/395], 21.0%). HIV was not associated with delayed fracture healing after IM nailing of the tibia or femur (multivariable odds ratio [OR]: 1·06; 95% confidence interval [CI]: 0·50–2·22). Participants with HIV had a statistically significant lower odds of non-union compared to HIV-negative participants (multivariable OR: 0·17; 95% CI: 0·01–0·92).

Conclusions: Fractures sustained in HIV-positive individuals can undergo surgical fixation as effectively as those in individuals who are HIV negative, with no increased risk of delayed union or non-union.

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Keywords: bone healing, delayed union, fracture, human immunodeficiency virus, intramedullary nailing, non-union, union

Introduction

Worldwide, approximately 38 million people are living with human immunodeficiency virus (HIV) infection.[1] Ninety-one percent of the people living with HIV reside in a low- or middle-income country (LMIC),[2] with an estimated 68% living in sub-Saharan Africa.[1] Widespread availability of antiretroviral therapy (ART) in sub-Saharan Africa since 2002 has altered the course and nature of the HIV epidemic, with HIV-positive individuals attaining healthy, close to normal life spans.[3]

Similar to the distribution of the HIV burden, it is estimated that 83% of injury-related deaths worldwide occur in LMICs, accounting for more deaths than those from malaria, tuberculosis and HIV combined.[4] For every injury-related death, it is estimated that 10 to 50 people sustain permanent or temporary disabilities: musculoskeletal trauma accounts for the majority of these injuries.[5] It is therefore likely that a considerable proportion of people presenting with musculoskeletal injuries in sub-Saharan Africa are HIV positive. However, the effects of the long-term

immunosuppression resulting from HIV infection on the fracture-repair process following a musculoskeletal injury are not well understood.

A number of factors could theoretically affect fracture healing. HIV principally affects immunological status by exhausting the host CD4 T cells, resulting in an increase in the risk of opportunistic infections. HIV also affects other cellular chemical mediators, including interleukins 1 and 6 (IL1, IL6), and tumour necrosis factor (TNF), which have been shown to play a role in the fracture-repair process.[6,7] HIV- and ART-associated interruption in osseous blood supply can also lead to osteonecrosis,[8,9] and this microvascular effect may lead to higher rates of delayed fracture healing and non-union.[10] Reduced bone mineral density, bone mineralisation, and bone turnover have also been shown to occur in HIV-positive individuals and those on ART.[11,12] This not only increases the risk of fragility fractures but could potentially influence fracture healing.[13]

A small number of clinical studies have investigated the role of HIV in the fracture-healing process.[14–16] These suggest that HIV and/or ART are associated with delayed fracture healing and may result in non-union, although patient numbers were small, and no underlying mechanisms were identified. If this hypothesis were shown to be true, the surgical management of fractures could be tailored to optimise bone union during the fracture-healing phase in HIV-positive patients, improving outcomes and reducing the substantial physical and social burden that occurs in these patients as a result of traumatic injuries.

Overall, the true effect of HIV and ART on bone healing is very poorly understood. This paper reports the findings of the HIV in Orthopaedic Skeletal Trauma (HOST) study, which aimed to investigate whether HIV infection is a risk factor for the development of delayed union or non-union following a fracture.

Methods

Study design and participants

The HOST study was a multi-centre prospective study of patients undergoing fracture surgery at two tertiary referral hospitals – Groote Schuur Hospital and Tygerberg Hospital – in Cape Town, South Africa. Recruitment was undertaken over a 14-month period, between September 2017 and December 2018.

Patients were eligible for inclusion if they were 18 years or older at assessment and had sustained a closed or open fracture of the shaft of the tibia or femur that was treated with intra-medullary (IM) nailing within two weeks of injury. Patients were excluded if they had a pathological fracture or a peri-trochanteric femur fracture (none shaft fractures); had major head injury or severe burns or were paraplegic; had pre-surgical infection at the fracture site or an open injury for >48 hours before the first debridement; or were unwilling to participate in study follow-up protocols, complete questionnaires, or attend follow-up. Participants who had sustained multiple injuries, including tibia or femur fractures, had their injuries documented and were included in the enrolment process.

The HOST study received ethical approval from the study sites, the University of Cape Town, the University of Stellenbosch Faculty of Health Science Human Ethics Committee and the Liverpool School of Tropical Medicine Research Ethics Committee. The study protocol has been published previously.[17]

Baseline

Participants were recruited post-operatively by one of two research nurses and undertook a baseline questionnaire to record clinical and sociodemographic characteristics, including risk factors for impaired bone healing and non-union (age, sex, smoking status, non-steroidal drug use, past medical history, vitamin D status, mechanism of injury, open fracture, injury severity score). Participants not confirmed to be taking ART were offered HIV testing (Alere Determine™ HIV-1/2 assay, Alere Medical Co. Ltd., Chiba, Japan and Uni-GoldTM Recombigen, Trinity BioTech, Wicklow, Ireland), with measurement of CD4 cell count (FACScount™, Becton Dickinson, BD Biosciences, San Jose, USA) and HIV viral load (bioMe'rieux NucliSENS EasyQ System HIV-1 QT) if they were found to be HIV positive. Participants newly diagnosed with HIV were linked to the HIV care clinics.

All participants were seen in clinic at 6 months post-surgery and were followed up for a minimum of 12 months. Outpatient assessments and x-rays were undertaken at 2 weeks, 6 weeks, 3 months, 6 months, and 9 months, to assess bone union. If a participant's fracture was confirmed to have united at 6 months, they were followed up by telephone at 9 months and 12 months. A non-union was confirmed if fracture union had not occurred at 9 months following injury. Participants with confirmed non-unions were offered further management, according to local protocols for treatment of non-union. If, at any time, the responsible consultant surgeon felt that there was a need for further surgery to achieve union before 9 months, this was offered following a joint discussion with at least two consultant orthopaedic surgeons.

Definitions and outcomes

The primary study outcome was the proportion of participants with delayed bone union at 6 months, compared between HIV-positive and HIV-negative participants. The secondary study outcomes were non-union at 9 months and infection.

Bone healing was assessed using the validated radiological union scoring system for the tibia (RUST scoring system).[18–20] Fracture union was defined as: radiological union on RUST score (score of three on at least three of the four cortices (anterior, lateral, medial, or posterior cortex) – a total RUST score of nine or more) within 6 months of surgery.[18–20] Delayed bone union was defined as impaired bone healing at 6 months on RUST score (RUST score <9).[18–20] Non-union was defined as either impaired bone healing at 9 months on RUST score (RUST score <9),[18–20] or the need for further surgery to achieve union (RUST score <9) before 9 months (decision made by two orthopaedic surgeons).

Two reviewers (both orthopaedic surgeons), blinded to HIV status, independently assessed radiological fracture union on radiographs. In case of discrepancies in RUST scoring between reviewers, a third reviewer (orthopaedic surgeon) independently undertook a review of the radiograph to determine the final outcome.

Infection was diagnosed using the United States Centers for Disease Control and Prevention (CDC) criteria for "superficial surgical site infection (SSI)" and "deep surgical site infection (DSI)". SSI was defined as wound infection involving the skin and subcutaneous tissue that occurred within 30 days of surgery,[21] and DSI as a wound infection involving the tissues deep to the skin that occurred within 30 days of injury (closed reduction of fracture) or 90 days (open reduction of fracture).[22] Late infection was diagnosed as any late wound breakdown (>30 days for closed reduction of fractures or >90 days for openly reduced fractures) or sinus formation, or unexplained late pain with associated radiological changes consistent with peri-implant infection.[23]

Statistical methods

A previously established orthopaedic surgical register suggested that 400 participants were likely to undergo IM nailing of the tibia and femur at the two centres over the 14-month study period and 80% (n = 320) were assumed to be able to complete follow-up to 9 months. On the basis of previous research,[24–26] it was estimated that 85% (n = 272) of the 320 participants would have fracture union at 6 months (control), and 15% (n = 48) would have delayed bone union (cases). Assuming that 20% of participants without delayed union would be HIV positive, a sample size of 400 participants would give 82·8% power to detect at least a two-times relative difference in HIV prevalence between cases and controls at the p=0·05 threshold.

Baseline characteristics were summarised using means (with standard deviations), medians (with interquartile ranges) and percentages, and compared between HIV-positive and HIV-negative participants. For the primary outcome (delayed union), a multivariable logistic regression model was constructed to estimate the odds ratio (OR) and 95% confidence interval (CI) for delayed union comparing HIV-positive and HIV-negative participants and adjusting for important confounders, identified *a priori* through construction of putative causal diagrams. A separate model was constructed for Participants with HIV only, to estimate the associations between HIV-associated predictors (e.g. CD4 cell count, viral load, ART use) and delayed union. For the secondary outcome (non-union), a multivariable logistic regression model was constructed to estimate the OR and 95% CI for non-union comparing HIV-positive and HIV-negative participants and adjusting for important confounders. Statistical analysis was done using *R* statistical software.

Some of the enrolled participants had more than one tibia or femur fracture. Therefore, in the analysis, confidence intervals were adjusted for clustering by including a random effects term in regression models.

This study was registered with ClinicalTrials.gov, Identifier: NCT03131947.

Role of funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between September 2017 and December 2018, 638 patients underwent 683 IM nailings of the femur and tibia at the two study sites and were screened for study eligibility; 238 participants (241 IM nailings) did not meet the study inclusion criteria and 400 participants (442 IM nailings) were enrolled in the study (Figure 1). Baseline characteristics of all participants are presented in Table 1.

The overall prevalence of HIV in the study population was 18·8% (75/400 participants). The 75 participants with HIV underwent 87 IM nailings, giving an overall prevalence of HIV per IM nail of 19·7% (87/442). Just over half of participants with HIV (42/75, 56·0%) knew their HIV diagnosis prior to enrolment in the study. The median length of

time a participant had had a diagnosis of HIV was 1397 days (inter-quartile range [IQR] 686–3565 days), or 3·8 years (IQR range 1·9–9·8 years). The remaining participants were diagnosed during their admission (25/75, 33·3%) or within 2 weeks of their discharge (8/75, 10·7%). Baseline characteristics of participants, stratified by HIV status, are shown in Table 2.

All 442 fractures underwent reamed locked (proximally and distally) IM nailings across the two study sites. The procedures were undertaken predominantly by registrar or equivalent training level surgeons (98·4%, 435/442). A total of 99·1% of participants (438/442) had antibiotics prior to their surgical procedures, according to their hospital policy. Over half of the procedures were performed out of normal daytime (07:00–17:00) working hours (51·8%, 229/442).

There were 161 open fractures (36·4%) that required IM nailing across the two study sites. The majority of open fractures were Gustilo Anderson (GA) type I injuries (70·2%, 113/161) (Appendix 1,http://links.lww.com/QAI/B665). There were 95 gunshot wound (GSW) fractures and the majority of these resulted in GA type I injuries (96·8%, 92/95); 92 out of 161 (57·1%) open fractures were due to low-velocity GSW fractures. Following open injuries, 97·5% (157/161) of participants received antibiotics within 24 hours of their injury and all the participants were given antibiotics prior to their surgical procedure, according to hospital guidelines. A high proportion of participants with open fractures underwent IM nailing as a single procedure, without an initial washout, or application of external fixator (88·8%, 143/161). At both study sites, all patients with low-velocity GSW fractures had their bullet entry and exit wounds left to heal by secondary intention and were given 24 hours of intravenous antibiotics peri-operatively.

Of the 400 participants recruited to the study, 42 (10·5%, 47 IM nailings) were lost to follow-up before reaching a study outcome and were excluded from primary analysis. None of the 42 participants had developed a delayed or non-union or deep or superficial surgical site infection before being lost to follow-up. Four participants (four IM nailings) who were lost to follow-up were HIV positive.

The population for final analysis therefore included 358/400 (89·5%) participants, who underwent 395 IM nailings; all of whom were followed up for a minimum of 12 months. Of these, 71 participants (71/358, 19·8%) were HIV positive (83 IM nailings, 83/395, 21·0%).

Radiographic classification of fracture union

For the primary outcome of union, there were discrepant RUST scores in only 11/395 (2·8%) radiographs (inter-observer agreement: 97·7%, Kappa = 0·92). At 9 months, there were two discrepancies in 69 (2·9%) radiographs taken to determine the secondary outcome of non-union (inter-observer agreement 97·1%, Kappa = 0·94).

Primary outcome: delayed fracture union

Overall, 17·5% (69/395) of fractures had delayed union at 6 months (Table 3). No participant had more than one fracture that developed delayed union. Female participants made up 23·7% (85/358) of the study population and were significantly less likely on univariable analysis to have delayed union compared to male participants (OR: 0·38, 95% CI: 0·16–0·78; p=0·014). However, on multivariableanalysis, although delayed union was still less likely in the female population, this difference was not statistically significant (OR: 0·41, 95% CI: 0·17–1·01; p=0·053).

A total of 14·5% (12/83) of fractures in participants with HIV developed delayed union, compared to 18·3% (57/312) fractures in the HIV-negative cohort. On both univariable (OR: 0·76, 95% CI: 0·37–1·44; p=0·417) and multivariable logistic regression (OR: 1·06, 95% CI: 0·50–2·22; p=0·869), there was no statistically significant difference in delayed union between HIV-positive and HIV-negative participants.

A greater number of ART-naïve participants with HIV developed delayed union (23·3%, 7/30) compared to those who were taking ART (12·2%, 5/41; p=0·227). Baseline CD4 cell counts among participants with HIV who developed delayed union were similar to those for participants with HIV who did not develop delayed union (460 cell/mm^3, IQR: 366–477 vs. 413 cell/mm^3, IQR 295–673; p=0·400, respectively). The median baseline HIV viral load in participants with HIV who developed delayed union was significantly higher than in participants with HIV who's fractures healed (3·02 log_{10} copies/ml, IQR: 0·98–4·76 log_{10} copies/ml vs. 2·13 log_{10} copies/ml, IQR: 1·30–4·40 log_{10} copies/ml; p=0·001]). This measurement included participants with detectable and undetectable viral load.

Open fractures resulted in 28·5% (39/137) of all delayed bone union cases, compared to 11·6% (30/258) of closed injuries. Open fractures were associated with more than three-times greater odds of developing delayed bone union compared to closed fractures, in both univariable (OR: 3·02, 95% CI: 1·78–5·18; p=0·001) and multivariable (OR:

3·13, 95% CI: 1·74–5·63; p=0·001) The proportion ofopen fractures that developed delayed union was similar in HIV-positive (27·3%, 6/22) and HIV-negative (28·7%, 33/115) participants (univariable OR: 0·93, 95% CI: 0·31–2·49; p=0·89).

Secondary outcome: fracture non-union

At 9 months, 5·8% (23/395) of fractures had developed a non-union (Table 3). A higher percentage of fractures in HIV-negative participants (7·1%, 22/312) experienced non-union compared to participants with HIV (1·2%, 1/83). These associations were statistically significant in both univariable logistic (OR: 0·16, 95% CI: 0·01–0·78)and multivariable (OR: 0·17, 95% CI: 0·01–0·92) models.

Open fractures resulted in 65·2% (15/23) of all the non-unions. A total of 10·9% (15/137) of all open fractures developed a non-union, compared to 3·1% (8/258) of closed fractures. On multivariable analysis, non-union was nearly three times more likely following an open fracture (OR: 2·96, 95% CI: 1·16–8·07; p=0·026). The proportion of participants who developed non-union following an open fracture was lower in participants with HIV compared to those without (0% 0/22 vs. 13·0%, 15/115).

Secondary outcome: infection

A total of 5·3% (21/395) of cases developed DSIs (Table 4); 8·4% (7/83) of fractures in participants with HIV developed DSI compared to 4·5% (14/312) of participants without HIV. HIV status was not significantly associated with DSI following IM nailing in the univariable model (OR: 1·96, 95% CI 0·72–4·89; p=0·161) or in themultivariable model (OR: 2·59, 95% CI: 0·86–7·80; p=0·090). Threefractures in participants who developed DSI went on to delayed union; two of these were HIV positive (2/7, 28·6% vs. 1/14, 7·1%). No participants with HIV and one participant without HIV developed a non-union following DSI (0/7, 0% vs. 1/14, 7·1%).

Only 1·5% (6/395) of fractures developed an SSI (Table 4) ; owing to these low numbers, univariable and multivariable logistic regression analyses were not undertaken. The proportion of fractures that developed SSI in participants with HIV was 1·2% (1/83), compared to 1·6% (5/312) in participants without HIV. Two fractures that developed SSI subsequently went on to non-union (both HIV negative), and no cases went onto delayed union.

Late implant infection developed in 1·8% (7/395) of all fractures (Table 4). Of these late infections, 1·3% (5/395) were in fractures in participants with HIV, compared to 0·5% (2/395) in participants without HIV. The proportion of fractures that developed late infection in participants with HIV was 6·0% (5/83), compared to 0·6% (2/312) in participants without HIV. Two late infections developed delayed union, both of which were in HIV-positive individuals (2/5, 40·0% vs. 0/2, 0%) and one late infection in an HIV-negative participant developed non-union.

Discussion

To the authors' knowledge, this is the first large prospective study to assess the association between HIV infection and bone healing following a fracture. Previous small studies (fewer than seven participants) reported delayed union in people with HIV.[16,27] The present study showed that HIV-positive status was not associated with the development of delayed bone healing following an IM nailing of the tibia or femur among trauma patients in the Western Cape, South Africa. In fact, there were lower odds of fracture non-union in participants with HIV compared to HIV-negative participants. Previous studies had suggested non-union in 0–11% of fractures in HIV-positive individuals following surgical fixation of a fracture.[14]

Antiretroviral therapy regimen, CD4 count, and viral load at baseline were also not associated with a significant risk of delayed union in the study population of participants with HIV. However, a greater number of ART naïve participants and more of those with a higher viral load developed delayed union and a much larger, appropriately powered, study is required to investigate this further.

HIV was not associated with the development of delayed union or non-union in open fractures. There is little evidence surrounding the risk of delayed union and non-union following an open fracture in people with HIV in the current literature but non-union rates of between 10% and 43% have been reported in a small number of studies.[14]

Contrary to previous research, this study demonstrated that HIV status does not appear to affect the clinical outcome of fracture healing and may potentially lower the risk of non-union. This could be explained by a number of factors, including direct and indirect immunological effects of HIV on bone,[28,29] and/or characteristics of the study population. However, this remains speculative as the study did not investigate mechanisms of bone healing. It is also acknowledged that this study focused solely on individuals who underwent IM nailing of a lower limb long bone fracture. Therefore, our results may not translate to fractures at different sites of the musculoskeletal system, fractures treated by other methods of fixation or managed non-operatively.

Infection rates in the study population as a whole were similar to those published in the literature.[30] There was a low number of SSIs overall (1·5%, 6/395) in the study population, so it was difficult to make comparisons between HIV-positive and HIV-negative populations. The proportion of DSIs was higher in the participants with HIV (8·4%, 7/83) vs. 4·5%, 14/312); however, this difference was not significant on multivariable analysis (OR: 2·59, 95% CI: 0·86–7·80; p=0·090). If DSI and SSI were combined to give a rate of "early implant infection", participants with HIV had an early implant infection rate of 9·6% (8/83) compared to 6·1% (19/312) in the population of participants without HIV. Late implant infection occurred in a higher proportion of HIV-positive than HIV-negative participants (6·0%, 5/83 vs. 0·6%, 2/312). Overall, this suggests that infection was slightly more common in those who are HIV positive, but the relatively low numbers make it difficult to draw substantial conclusions

When assessing the role of infection and the development of delayed union and non-union, participants with HIV who developed either an SSI, DSI, or late infection were more likely to go onto delayed union (7/13, 53·8% vs. 1/21, 4·8%) but not non-union (0/13, 0% vs. 4/21, 19·0%). However, the prevalence of infection overall was too low to make definitive conclusions and much larger studies would be needed to investigate this further.

Of the seventy-five participants with HIV enrolled in the study 56% (42/75) were taking ART on enrollment. Ideally, in order to determine the effect of HIV infection alone on fracture healing, the study should have only included those participants who were not on ART therapy. However, ethical restrictions and time limitations made this impossible. Another limitation was the use of the RUST score to determine the primary outcome of delayed union. This scoring system has not been validated for use in the femur. However, it is the best tool available to determine bone union without the need for additional investigations.

This study demonstrates that HIV was not shown to be associated with the risk of developing delayed bone healing following an IM nailing of the tibia or femur in the study population. There was a strong trend towards lower odds of fracture non-union in participants with HIV compared to those who are HIV-negative. In conclusion, the evidence from this study suggests that fracture surgery in individuals with HIV is safe and as least as effective in HIV-positive as HIV-negative patients, with no increased risk of delayed or non-union. The results show that HIV status should not influence the decision to operate or use internal fixation in these patients.

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Figure 1. Flow diagram of study population recruitment - IM: intramedullary.

Table 1. Baseline characteristics of study participants, stratified by HIV status

Characteristic	Study cohort *N* = 400	HIV negative *N* = 325	HIV positive *N* = 75	p value
Sex, *n* (%)				
Male	313 (78·3)	262 (80·6)	51 (68·0)	0·030
Female	87 (21·7)	63 (19·4)	24 (32·0)	
Age, years: median (IQR)	32·36 (18–71)	31 (18–71)	35 (19–58)	0·080
BMI, kg/m$^{2:}$ median (IQR)	23·02 (15·54–51·19)	22·9 (15·72–47·5)	23·31 (15·55–51·2)	0.720
Fracture site[a], *n* (%)				
Tibia	215 (48·6)	171 (48·2)	44 (50·6)	0·460
Femur	227 (51·4)	184 (51·8)	43 (49·4)	
Open fracture[a], *n* (%)				
Yes	161 (36·4)	139 (39·2)	22 (25·3)	0·059
No	281 (63·6)	216 (60·8)	65 (74·7)	
Number of IM nailing's performed per participant, *n* (%)				
1 nail	361 (90·3)	296 (91·1)	65 (86·7)	0·340
2 nails	37 (9·3)	28 (8·6)	9 (12·0)	
3 nails	1 (0·2)	1 (0·3)	0	
4 nails	1 (0·2)	0	1 (1·3)	
Drinks <u>any</u> alcohol, *n* (%)				
Yes	223 (55·8)	181 (55·7)	42 (56·0)	0·940
No	177 (44·2)	144 (44·3)	33 (44·0)	
Smoking status, *n* (%)				
Non-smoker	175 (43·8)	134 (41·2)	41 (54·7)	0·050
Smoker	225 (56·2)	191 (58·8)	34 (45·3)	
Transfer from district hospital, *n* (%)				
Yes No	98 (24·5) 302 (75·5)	74 (22·8) 251 (77·2)	24 (32·0) 51 (68·0)	0·100
Time taken to arrive at treating hospital, hours: median (IQR)	9 (4–24)	10 (4–24)	12 (6–18)	0·840
Patient-reported outcome measure (PROMs)				
DRI pre-op, median (IQR)	0 (0–34·3)	0 (0–28)	0 (0–34·3)	0·090

BMI: body mass index; DRI: Disability Rating Index; HIV: human immunodeficiency virus; IM: intramedullary; IQR: interquartile range.

[a] *N* = 442 for study cohort, 355 HIV negative, 87 HIV positive.

Table 2. Baseline characteristics of HIV-positive participants

HIV status (*N* = 400)	
Positive	75 (18·8)
Negative	325 (81·2)
HIV parameter (*N* = 75)	
Diagnosis, *n* (%)	
Before admission	42 (56·0)
On or during admission	25 (33·3)
After discharge	8 (10·7)
Age at time of HIV diagnosis, years: median (IQR)	32·36 (17·46 – 48·23)
Length of time with HIV diagnosis*, days: median (IQR)	1397 (686–3565)
Taking ART on admission, *n* (%)	
Yes	42 (56·0)
No	33 (44·0)
Length of time taking ART therapy, days: median (IQR)	1732 (678–3568)
ART (*N* = 42), *n* (%)	
TDF, 3TC + EFV	38 (90·5)
TDF, FTC + EFV	1 (2·4)
ZDV, 3TC + LPV/r	3 (7·1)
CD4+ count on admission, cells/mm^3: median (IQR)	393 (63–1145)
Viral load (cps/ml) on admission, $\log_{10}$ copies/ml: median (IQR)	2·13 (1·3–4·62)

ART: antiretroviral therapy; cp: copies; EFV: efavirenz; FTC: emtricitabine HIV: human immunodeficiency virus; IQR: interquartile range; LPV/r: lopinavir/ritonavir; 3TC: lamivudine; TDF: tenofovir; ZDV: zidovudine.

*Participants with a prior diagnosis of HIV before admission

Table 3. Associations between HIV status and fracture delay or non-union

	HIV positive (*N* = 83), *n* (%)	**HIV negative (*N* = 312), *n* (%)**	**Univariable odds ratio (95% confidence interval)**	**Multivariable odds ratio (95% confidence interval)**
Delayed union at 6 months	12 (14·5)	57 (18·3)	0·76 (0·369–1·44)	1·06 (0·50–2·22)[a]
Non-union at 9 months	1 (1·2)	22 (7·1)	0·16 (0·01–0·78)	0·17 (0·01–0·92)[b]

[a]Adjusted for age, sex, smoking status, open fracture status, deep surgical site infection, vitamin D level and fracture site.

[b]Adjusted for age, sex, smoking status, open fracture status, haemoglobin level and vitamin D level.

Table 4. Outcomes of infection, stratified according to HIV status

	HIV positive (*N* = 83), *n* (%)	**HIV negative (*N* = 312), *n* (%)**
Deep surgical site infection, *n* (%)	7 (8·4)	14 (4·5)
Superficial surgical site infection, *n* (%)	1 (1·2)	5 (1·6)
Late infection, *n* (%)	5 (6.0)	2 (0·6)

Figure 1. Flow diagram of study population recruitment - IM: intramedullary.