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Is human immunodeficiency virus a risk factor for the development of nonunion?—a case–control study

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Abstract

Objective: Human immunodeficiency virus (HIV) infection has been suggested to be associated with an increased risk of the development of nonunion after a fracture. This prospective matched case–control study in South Africa investigated common risk factors, including HIV status, that influence the development of a nonunion after a femur or tibia fracture.

Methods: Adult participants (cases) with established nonunions of the femur or tibia shaft were recruited over a 16-month period, between December 2017 and April 2019. They were matched for (1) age; (2) sex; (3) fracture site; and (4) fracture management type, with "control" participants who progressed to fracture union within 6 months of injury. All participants were tested for HIV. Multivariable logistic regression models were constructed to investigate associations between known risk factors for the development of nonunion and impaired fracture healing.

Results: A total of 57 cases were matched with 57 "control" participants (44/57 male, 77.2% vs. 13/57 female, 22.8%, median age 36 years). HIV status was not associated with the development of nonunion after the management of tibia and femur fractures, on both univariate (odds ratio, 0.40; confidence interval, 0.10–1.32; $P = 0.151$) or multivariable (odds ratio, 0.86; confidence interval, 0.18–3.73; $P = 0.831$) analysis. No other confounding factors were shown to have any statistically significant impact on the odds of developing nonunion in this study cohort.

Conclusion: This study demonstrates that HIV does not seem to increase the risk of the development of nonunion and HIV-positive individuals who sustain a fracture can be managed in the same manner as those who are HIV negative.

Key Words: bone healing, delayed union, fracture, human immunodeficiency virus, intramedullary nailing, nonunion, union

The authors declare no conflicts of interest.

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The authors consent to the publication of our work.

All study data are available to review on request.

This study received ethical approval from the study sites, the University of Cape Town, the Stellenbosch University Faculty of Health Science Human Ethics Committee, and the Liverpool School of Tropical Medicine Research Ethics Committee.

All authors contributed to all or in part to the study concept, design, data collection, data analysis, or study write-up

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1. Introduction

Fracture healing is a multifactorial process affected by a number of biological factors, injury characteristics, and fracture fixation mechanics.[1–2] In particular, human immunodeficiency virus (HIV) has been suggested to be associated with an increased risk of the development of delayed and nonunion.[3–6]

Approximately 35.3 million people are living with HIV globally, with the highest prevalence seen in sub-Saharan Africa.[7] In South Africa, HIV prevalence is high (18.9%) among the adult general population (aged 15–49 years) and estimates suggest that around 1 in 5 patients with trauma are HIV positive.[8] HIV and its treatment have both been shown to result in a number of musculoskeletal manifestations, including a reduction in bone mineralization, bone mineral density, and bone turnover, causing osteoporosis and osteonecrosis.[9–13]

In the mid-1990s, concerns were first raised regarding potential problems with HIV-positive patients undergoing fracture fixation.[14] Both clinical and basic science research have suggested HIV infection may be associated with problems with fracture healing and nonunion.[3] However, the true effect of HIV on fracture healing is unclear, with recent evidence demonstrating no association between HIV and the development of delayed or nonunion after internal fixation of lower limb fractures.[15]

The aim of this study was to determine whether HIV status influenced the development of a nonunion after a femur or tibia fracture in South Africa.

2. Materials and Methods

2.1. Study Design and Participants

This was a multicenter, case–control study performed at 2 tertiary referral hospitals in Cape Town, South Africa—Groote Schuur Hospital and Tygerberg Hospital. Patients presenting with a nonunion (cases) of the femur or tibia fracture were matched with patients who had fractures that had united. Recruitment was undertaken over a 16-month period, between December 2017 and April 2019.

Patients were eligible for inclusion if they were 18 years or older at assessment and had sustained a closed or open extra-articular fracture of the tibia or femur and had undergone a single course of management for their fracture. Patients were excluded if they had a pathological fracture or evidence of infection at the fracture site at the time of assessment. This was assessed by a qualified and fellowship-trained orthopaedic surgeon (S.M.G.). Those unable to consent for inclusion in the study were also excluded.

This study received ethical approval from the study sites, the University of Cape Town, the Stellenbosch University Faculty of Health Science Human Ethics Committee, and the Liverpool School of Tropical Medicine Research Ethics Committee.

2.2. Baseline

Cases were prospectively recruited from trauma clinics, emergency admissions, and tertiary referrals at the 2 study sites. Once a case was recruited, a matched control was prospectively identified from the same sources to be included in the study. One of 2 research nurses undertook a baseline questionnaire to record clinical and sociodemographic characteristics, including risk factors for impaired bone healing and nonunion (age, sex, smoking status, nonsteroidal drug use, medical history, mechanism of injury, open fracture, injury severity score). Participants not taking antiretroviral therapy (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) 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 HIV care clinics. All participants included in the study underwent a HIV test.

Bone healing was assessed using a validated x-ray scoring system—the Radiological Union Scale for Tibial Fractures (RUST scoring system).[16,17]

2.3. Matching

Cases were matched in a 1:1 ratio with controls on the following criteria.

a. Age: ±10 years
b. Sex:
    - Male
    - Female
c. Injury:
    - Tibia
    - Femur
d. Management of fracture:
    - IM nailing
    - Open reduction and internal fixation with plate and screw fixation
    - Ilizarov external fixator frame
    - Hexapod external fixator (Taylor spatial frame)
    - Nonoperative management

Each "case" was matched with a single "control." Once a "control" had been enrolled, they were not eligible for matching with another "case." All "cases" and "controls" presented and were treated within the same period the study was performed (December 2017 and April 2019). All matching was performed by a single researcher (S.M.G.) blinded to all parameters, other than those required for the matching process, at the time of enrollment. This included being blinded to the participants' HIV status.

2.4. Outcome Definitions

Fracture union was defined as radiological union on RUST score (score of 3 on at least 3 of the 4 cortices [anterior, lateral, medial, or posterior cortex]—a total RUST score of 10 or more) within 6 months of surgery.[18–20] Nonunion was defined as either impaired bone healing at 9 months on RUST score[18–21] or the need for further surgery to achieve union (RUST score <9) before 9 months (decision made by 2 orthopaedic surgeons).

Two reviewers (both qualified and fellowship-trained orthopaedic surgeons), blinded to bone union outcome status, independently assessed radiological fracture union on radiographs. Fracture nonunions were summarized into 2 main types by the 2 reviewers: hypertrophic and atrophic/oligotrophic.[22] 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 and nonunion definition.

2.5. Sample Size Calculation

Sample size calculation for the case-control study used the methodology described by Dupont[23] and included the Fleiss[24] correction for matched case–control design. Assuming that 20%

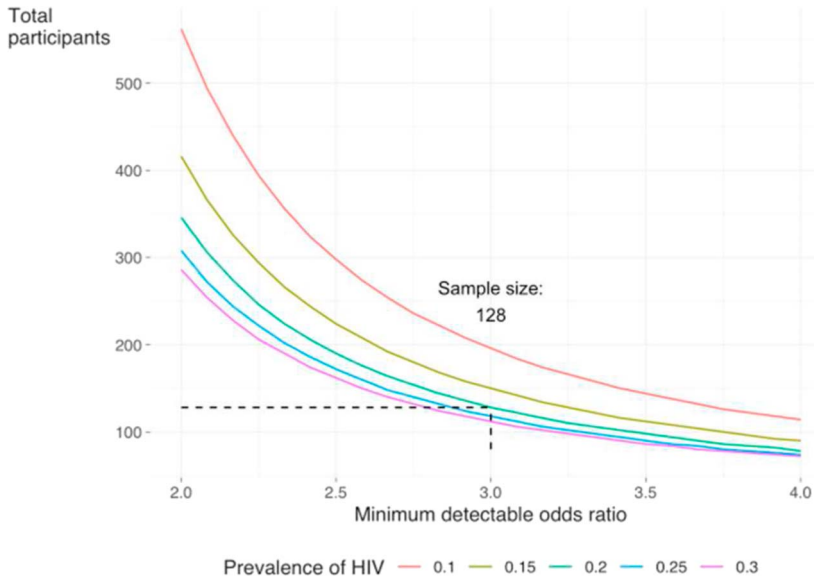

Figure 1. Sample size calculation.

of the controls would be HIV positive,[25,26] a total sample size of 128 (64 cases and 64 controls) would give 80% power to detect at least an odds ratio (OR) of 3.0 for nonunion, comparing between the case and control groups (Fig. 1).

2.6. Statistical Analysis

Distributions of baseline characteristics were summarized using means, medians, proportions, and distributional measures (standard deviations and interquartile ranges), tabulated and plotted and compared between the exposure (case) group and nonexposure group (control). Missing data were reported in tables of baseline characteristics. For the primary outcome (nonunion), confirmation was made that there were sufficient matching strata between the case and controls by cross-tabulation.[27] A multivariable logistic regression model was then constructed to estimate the OR and 95% confidence interval (CI) for nonunion comparing between case and control participants and adjusting for matching characteristics, and additional important confounders identified *a priori* through the construction of putative causal diagrams. In constructing multivariable models, we compared estimates obtained from complete case analysis and after multiple imputations of missing values. Parameters and confounding factors included in the univariate and multivariable logistic regression model included: HIV status, age, sex, fracture management, fracture site, smoking status, open fracture, hemoglobin (>6 months postfracture), and vitamin D at baseline.

Analysis of difference between continuous and categorical data not using logistic regression analysis was assessed using the *t* test or the χ^2 test, respectively. All statistical analysis was undertaken using "R" statistical computing software.

2.7. 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.

3. Results

Between December 2017 until April 2019, 83 participants were identified with established nonunions of the tibia or femur and

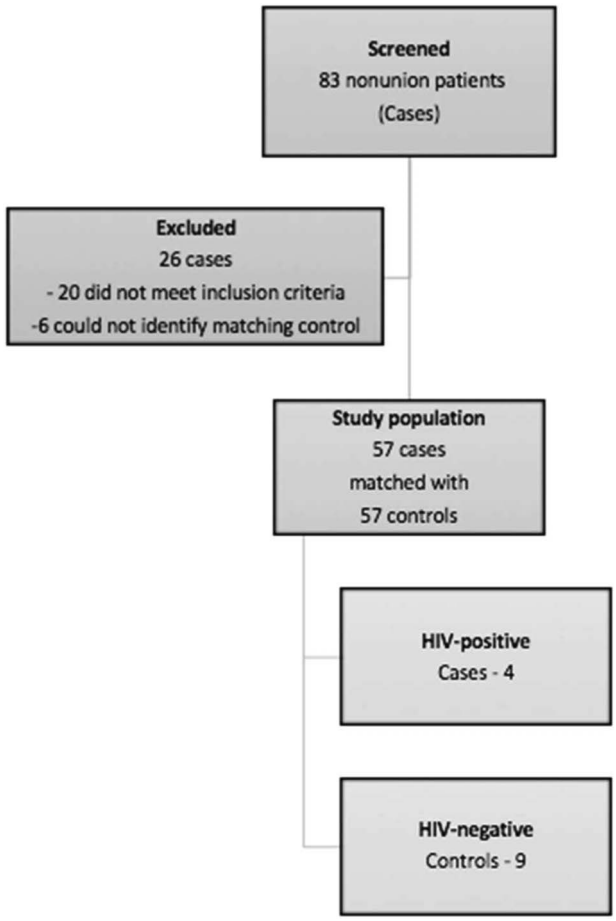

Figure 2. Flow diagram of study population recruitment.

TABLE 1

Baseline Characteristic of HIV-Positive Participants

HIV Parameter	Cases (Nonunion), n = 57 (%)	Controls (Union), n = 57 (%)	*P* (Univariate Regression)
HIV status			0.200
Positive	4 (7.0)	9 (15.8)	
Negative	53 (92.0)	48 (84.2)	
Age at time of HIV diagnosis* (median, IQR, years)	39.16 (27.25–52.4)	39.24 (27.9–45.21)	1.00
Taking ART on admission*			
Yes	3 (75.9)	5 (55.5)	0.502
No	1 (25.0)	4 (44.4)	
Length of time taking ART therapy† (days: mean)	1376 (1242–1450)	1172 (683–1805)	0.450
$CD4^+$ count (cell/mm^3)* (median, IQR)	569 (520–683)	393 (337–610)	0.200
Viral load (cps/mL)* (log^{10}, median, IQR)	0.65 (0–2.00)	2.56 (1.30–4.68)	0.300

ART, antiretroviral therapy; cps, copies; IQR, interquartile range.
* n = 4/9.
† n = 3/5.

were screened and considered for inclusion in the study. Twenty participants did not meet the study inclusion criteria and were not enrolled (Fig. 2). The predominant reason for participants not being enrolled was that they had infected nonunions (15/20, 75%) or the participant declined to participant in the study (5/20, 25%). A further 6 participants were excluded because it was not possible to identify matched controls.

TABLE 2

Baseline Characteristics of Study Population

Characteristics	Cases (Nonunion), n = 57 (%)	Controls (Union), n = 57 (%)	*P*
Sex			1.00
Male	44 (77.2)	44 (77.2)	
Female	13 (22.8)	13 (22.8)	
Age (years: median, IQR)	36 (21–76)	36 (18–63)	0.530
Fracture site			1.00
Tibia	37 (63.2)	37 (63.2)	
Femur	20 (36.8)	20 (36.8)	
Management			1.00
Plaster	3 (5.3)	3 (5.3)	
IM nailing	36 (63.2)	36 (63.2)	
Plate and screw fixation	2 (3.5)	2 (3.5)	
Circular fixator	16 (28.1)	16 (28.1)	
Hexapod	4 (25.0)	4 (25.0)	
Ilizarov	12 (75.0)	12 (75.0)	
Alcohol			0.99
Yes	24 (42.1)	25 (43.9)	
No	33 (57.9)	32 (56.1)	
Smoking			0.577
Nonsmoker	23 (40.4)	26 (45.6)	
Smoker	34 (59.6)	31 (54.4)	
Cigarettes per day*			0.600
0–5	8 (23.5)	7 (22.6)	
6–10	13 (38.2)	14 (24.6)	
11–20	8 (23.5)	7 (22.6)	
>20	5 (14.7)	3 (5.3)	
Duration of smoking history*			0.912
<1 y	0	0	
1–5 y	3 (8.8)	4 (12.9)	
5–10 y	7 (20.6)	11 (35.5)	
>10 y	24 (70.6)	16 (51.6)	
Patient-reported outcome measure			0.001
DRI (median, IQR)	45.2 (0–107.8)	24.5 (0–96.1)	

DRI, disability rated index; IM, intramedullary; IQR, interquartile range.
* Cases, n = 34; controls, n = 31.

The main study cohort of 57 cases were matched with 57 "control" participants. Most of the participants were male (44/57 male, 77.2% vs. 13/57 female, 22.8%), with a median age of 36 years in each group. Thirty-seven tibia and 20 femoral fractures were enrolled, and the main form of initial treatment for the fractures was IM nailing (36/57, 63.2%). There were 16 circular fixators (28.1%) enrolled, 3 fractures managed with open reductions and internal fixations with plates and screws (5.3%) and 3 (3.5%) fractures treated conservatively.

Of the 57 nonunion cases, 7.0% (4/57) occurred among HIV-positive participants, while 15.7% (9/57) of the controls were HIV positive. A slightly higher proportion of HIV-positive cases were taking ART compared with the controls (3/4, 75% vs. 5/9, 55.5%; $P = 0.502$) (Table 1).

There was a similar proportion of smokers in the "control" group compared with the "case" group (26/57, 45.6% vs. 23/57, 42.1%), with no statistical significance between the groups ($P = 0.7$). As expected, the disability rated index was lower in the "control" group compared with the participants with nonunion (24.5 vs. 45.2, $P = 0.001$). The basic demographics and characteristics of the study participants are summarized in Table 2.

There was a higher proportion of open fractures in the "control" group compared with the participants with nonunion, although this difference was not statistically significant (28/57, 49.1% vs. 22/57, 38.6%, $P = 0.300$) (Table 3).

3.1. Radiographic Classification of Fracture Union

The interobserver agreement, between reviewers 1 and 2, of the outcome of union or nonunion using the final RUST score was 96.5% (Kappa = 0.93). The reviewers also determined the type of nonunion a participant had developed (hypertrophic or atrophic/oligotrophic). The interobserver agreement between the 2 reviewers was 100% (Kappa 1).

There were 32/57 (56.1%) atrophic and 25/57 (43.9%) hypertrophic nonunions in the "case" study cohort.

3.2. Risk Factors for the Development of Nonunion

On univariate and multivariable logistic regression analysis, HIV was not statistically associated with the development of a nonunion in the study population (univariate OR, 0.40; CI, 0.10–1.32; $P = 0.151$; multivariable OR, 0.85; CI, 0.18–3.73; $P = 0.831$).

The hemoglobin level was lower in the "control" group (median 9.8 per 1g/dL; CI, 8.02–11.6) participants than among participants with fracture nonunion (median 13.2 per 1g/dL; CI,

TABLE 3

Open Fractures, Mechanism, and Injury Severity Score of Study Population

	Cases n = 57 (%)	Controls n = 57 (%)	*P*
Open fracture			0.300
Yes	22 (38.6)	28 (49.1)	
No	35 (61.4)	29 (50.9)	
Gustilo Anderson classification*			0.700
I	10 (45.5)	11 (39.3)	
II	1 (4.5)	3 (10.7)	
IIIA	9 (40.9)	9 (32.1)	
IIIB	2 (9.1)	5 (17.9)	
IIIC	0 (0)	0 (0)	
Injury severity score ≥16			0.800
Yes	13 (22.8)	15 (26.3)	
No	44 (77.2)	42 (73.7)	
Low energy	1 (1.8)	5 (8.8)	0.080
High energy	5 (8.8)	1 (1.8)	
Motor vehicle accident—car/motorbike/truck	16 (28.1)	10 (17.5)	
Motor vehicle accident—pedestrian	25 (43.9)	24 (42.1)	
Gunshot wound	9 (15.8)	11 (19.3)	
Low energy	9 (100.0)	10 (90.9)	
Medium energy	0	1 (9.1)	
High energy	0	0	
Blunt	0	4 (7.0)	
Crush	1 (1.8)	2 (3.5)	
Simple—stable			0.600
A2	11 (19.3)	4 (7.0)	
A3	11 (19.3)	9 (15.8)	
B2	7 (12.3)	12 (21.1)	
Total	29 (50.9)	25 (43.9)	
Complex—unstable			
A1	2 (3.5)	9 (15.8)	
B1	4 (7.0)	8 (14.0)	
B3	7 (12.3)	3 (5.3)	
Total	13 (22.8)	20 (35.1)	
Comminuted—highly unstable			
C1	4 (7.0)	1 (1.8)	
C3	7 (12.3)	7 (12.3)	
Total	11 (19.3)	8 (14.0)	
Segmental—potentially unstable			
C2	4 (7.0)	4 (7.0)	
Total	4 (7.0)	4 (7.0)	
Winquist classification, femur (n = 20)			0.300
Type 0	4 (20.0)	4 (20.0)	
Type 1	3 (15.0)	3 (15.0)	
Type 2	6 (30.0)	6 (30.0)	
Type 3	3 (15.0)	3 (15.0)	
Type 4	4 (20.0)	4 (20.0)	

IQR, interquartile range.
* n = 22/28.

11.6–14.3). The univariate (OR, 1.55; CI, 1.31–1.89; $P = 0.001$) and multivariable analysis (OR, 1.64; CI, 1.33–2.09; $P = 0.001$) confirmed that higher hemoglobin levels were associated with fracture nonunion.

Vitamin D levels were slightly lower in control (median 50.4 per 1 nmol/L; CI, 39.5–60.0) participants than in the cases (median 59.65 per 1 nmol/L; CI, 44.8–73.6), but both were within the acceptable range (Fig. 3). Univariate analysis (OR, 1.03; CI, 1.01–1.05; $P = 0.005$) showed that the higher the level of vitamin D levels were associated with nonunion, but on multivariable analysis, this association was attenuated (OR, 1.02; CI, 1.00–1.05; $P = 0.069$). Age, sex, or smoking was not shown to be associated with the development of nonunion on both univariate and multivariable analysis (Table 4).

4. Discussion

The findings from this study suggest that HIV is not a risk factor for the development of nonunion.[15] There was an overall HIV prevalence of 11.4% (13/114) in the study population. A prevalence of HIV in a similar cohort of patients has been shown to be 19.8% (71/358 participants), and the national prevalence of HIV in South Africa is approximately 18.9%.[8,15,28] However, the prevalence in the Western Cape, where the study was undertaken, is much less at 5.6%.[8,28]

The hemoglobin (9.8 vs. 13.2*g*/dL; $P = 0.2$) and vitamin D (50.35 vs. 59.65 nmol/L; $P = 0.4$) levels were all lower in the "control" compared with the cases, although none of the differences between the groups were statistically significant. Both these blood parameters have been linked to problems with fracture healing and nonunion in in vivo animal research.[29–35] Therefore, these findings are contrary to what would have been expected, with lower levels of hemoglobin and vitamin D anticipated in the nonunion cohort.

Any effect on fracture healings that may result from lower levels of vitamin D, albumin, and hemoglobin are likely to only be evident at the extreme ends of the values for each blood parameter. For example, vitamin D level in the cases and controls was within the "normal" range and not <25 nmol/L used by the National Institute for Health and Care Excellence as a definition of vitamin D deficiency.[36] Therefore, essentially, the values of vitamin D were very similar between each group and of limited clinical significance.

The higher the level of hemoglobin a participant had, the more likely they were to have a nonunion may be explained by the difference in the time between the date of injury and enrollment into the study for the cases compared with the controls (320 days [276–523] vs. 180 [122–241]; $P = 0.001$). Cases had longer time to recover from their injury and any surgery, potentially leading to higher hemoglobin levels.

There is strong evidence demonstrating the link between smoking, particularly nicotine, to problems with fracture healing and smoking has been demonstrated to reduce angiogenesis in the early stage of fracture healing.[37,38] However, Starlinger et al[39] reported that age and sex have a greater effect on the key osteoprotegerin/RANKL pathway than smoking, which may explain the findings in this study population, in which smoking was not found to be associated with the development of nonunion on multivariable analysis (OR, 1.24; CI, 0.47–3.30; $P = 0.662$). Of note, in this study, a clear majority of the smokers were smoking less than 10 per day, whereas smoking a pack per day (>10 cigarettes per day) has been to result in a hypoxic state for the whole day and this may help explain the lack of an association with nonunion in this study.[40] We also excluded infected nonunions, and it is possible that smoking has a greater effect on the development of deep infection, which predisposes to nonunion.

A higher proportion of open fractures was seen in the "control" group compared with the cases (28/57, 49.1% vs. 22/57, 38.6%; $P = 0.3$). It would be expected that the number of open fractures would be higher in the "case" group, rather than the "control" because there is established evidence that open fractures have a higher rate of nonunion.[22,41,42] As we matched for treatment and the treatment was affected by the open status of the fracture, we would have partially matched for open status.

The energy of the injury and the pattern of the subsequent fracture played a significant role in the likelihood of fracture healing. Although, where possible fractures were matched for OTA/AO classification, this was not the case for all injuries. It would be expected that the number of patients with an injury

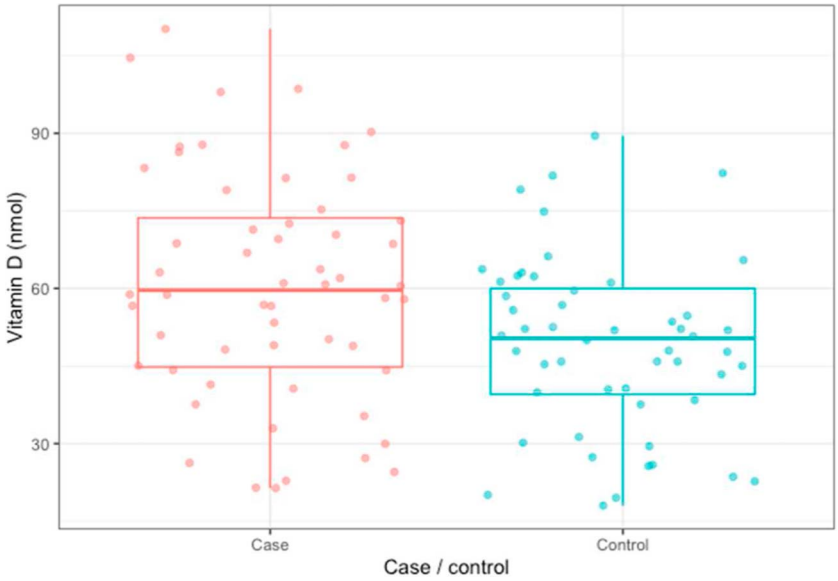

Figure 3. Vitamin D level of the fracture nonunion "case" and fracture union "control" groups.

severity score greater than 16 and more complex and/or unstable fractures according to the OTA/AO classification would be higher in the cases. However, the control group had more complex fracture patterns (cases 23 vs. control 32) and more patients with an injury severity score greater than 16 (cases 13 vs. control 15). Although, none of these differences were statistically significant.

4.1. Limitations of This Work

Our sample size calculation anticipated a prevalence of 20% of HIV in the "control" group. In the general trauma population in the same patient population, the rate of HIV in South Africa has been shown to be 18%–20%.[15] Overall, the rates of HIV in the "control" group were significantly lower than anticipated. For this reason, the study team stopped recruitment before reaching the sample size target because it was recognized that even if the sample size of 64 was reached, the HIV prevalence would still have been lower than the 20% predicted. In a case-cohort study by our research team, we demonstrated that HIV was not shown to be associated with the risk of developing delayed bone healing after an IM nailing of the tibia or femur. In fact, there was a strong trend toward lower odds of fracture nonunion in HIV-positive

TABLE 4

Risk Factors for the Development of Nonunion in the Study Population

	Cases—Nonunion, n = 57, %	Controls—Union, n = 57, %	Univariate Odds Ratio (95% CI)	*P*	Multivariable Odds Ratio (95% CI)	*P*
HIV status						0.831
HIV negative	53 (92.0)	48 (84.2)				
HIV positive	4 (7.0)	9 (15.8)	0.40 (0.10–1.32)	0.151	0.85 (0.18–3.73)	
Age (per year)	36 (21–76)	36 (18–63)	1.01 (0.98–1.04)	0.530	1.01 (0.97–1.06)	0.593
Sex						0.155
Male	44 (77.2)	44 (77.2)				
Female	13 (22.8)	13 (22.8)	1.00 (0.41–2.41)	1.000	2.36 (0.74–8.09)	
Fracture management						0.236
Plaster	3 (5.3)	3 (5.3)	1.00 (0.792–1.26)	1.000	1.21 (0.89–1.66)	
IM nailing	36 (63.2)	36 (63.2)				
Plate + screws	2 (3.5)	2 (3.5)				
Circular fixator	16 (28.1)	16 (28.1)				
Fracture site						
Femur	37 (63.2)	37 (63.2)	1.00 (0.43–2.16)	1.00	0.348 (0.10–1.05)	0.071
Tibia	20 (36.8)	20 (36.8)				
Smoking status	20 (36.8)	20 (36.8)				0.662
Yes	23 (40.4)	26 (45.6)	1.24 (0.59–2.62)	0.577	1.24 (0.47–3.30)	
No	34 (59.6)	31 (54.4)				
Open fracture						0.716
Yes	22 (38.6)	28 (49.1)	0.65 (0.31–1.37)	0.258	1.21 (0.43–3.57)	
No	35 (61.4)	29 (50.9)				
Hemoglobin (IQR, per 1 g/dL)	13.2 (11.6–14.3)	9.8 (8.02–11.6)	1.55 (1.31–1.89)	0.001	1.64 (1.33–2.09)	0.001
Vitamin D (IQR, per 1 nmol/L)	59.65 (44.8–73.6)	50.4 (39.5–60.0)	1.03 (1.01–1.05)	0.005	1.02 (1.00–1.05)	0.069

CI, Confidence intervals; IQR, interquartile range.

participants compared with HIV-negative participants, although this was in a small sample of 23 nonunions.[15] This could explain the low rate of HIV in our "case" group, further supporting our study conclusions, but we acknowledge that further research is needed and any conclusions need to be interpreted with caution.

The presence of established infection at the fracture site was an exclusion criterion. However, in a high proportion of nonunions, up to 40% have an undiagnosed underlying infection.[22] If the fractured limb appeared infection-free on inspection, no microbiology assessment was included in the diagnosis of nonunion. No intraoperative microbiology samples after nonunion surgery were assessed. Therefore, some of the cases included could have been undiagnosed infected nonunions.

Fracture healing is a multifactorial process, and it is possible that we did not include all parameters that may influence the fracture healing process in our analysis.

5. Conclusion

We have demonstrated that HIV does not seem to increase the risk of the development of a nonunion in this study cohort. It is important to note that 75% of the HIV-positive patients who developed nonunion were on ART, raising the possibility that the treatment rather than the disease might affect the healing process. However, this area requires further investigation. No other confounding factors were shown to have any statistically significant impact on the odds of developing nonunion in this study cohort.

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