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Fracture management in HIV positive individuals: A systematic review

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Full Title:	Fracture management in HIV positive individuals: A systematic review
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Abstract:	Abstract Purpose: Human immunodeficiency virus (HIV) infection could potentially play an important role in the management of fractures as they have been shown to affect fracture healing and the post-operative risk of implant sepsis. Methods: A systematic review of the relevant literature was performed on PubMed and Scopus databases. Twenty-six studies were identified, critiqued and analysed accordingly. No randomised controlled trials were identified. Results: HIV positivity was not shown to influence an individual's risk of early wound infection in operatively managed closed fractures. The rate of pin track infection in open injuries managed with external fixators was low. However, in open injuries managed with internal fixation, early wound infection rates were increased in the HIV-positive population compared to HIV-negative individuals. Regarding late implant infection, in closed fractures there appeared to be no increased risk of infection but there is limited evidence for open injuries. Additionally, further evidence is needed to establish if the rate of union in both open and closed fractures are influenced by HIV status. Conclusion: Overall, no evidence was found to suggest that surgical management of fractures in the HIV population should be avoided, and fixation of closed fractures in the HIV population appeared to be safe. The effect of anti-retroviral therapy is unclear and this should be further researched. However, based on the limited evidence, caution should be taken in the management of open fractures due to the potentially increased infection risk. The impact of anti-retroviral therapy on the outcomes of surgery needs further evaluation.
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	Thank you for your kind comments on our unique systematic review. We have responded to the reviewers and made the changes suggested. Kind regards, Authors
Response to Reviewers:	International Orthopaedics Fracture management in HIV positive individuals: A systematic review Response to reviewers All changes to the paper have been highlighted by underlining the text. Reviewer #1: Well written review on an important topic from a good center with strong backup and experience of monitoring of the disease. The authors present a systematic review on the risks and complications of fracture treatment in HIV patients. The systematic review follows the PRISMA guidelines and the standard methodology for systematic reviews. The topic is interesting and important. The manuscript is well written and presented. The methodology is good. The weaknesses of the paper are identified and recognized. The conclusions are pertinent. Bibliography is up to date and pertinent to the topic. You may consider reading and including the following references from "Intl Orthop" after formatting in the Journal style - Menendez ME, Memtsoudis SG, Opperer M, Boettner F, Gonzalez Della Valle A. (2015) A nationwide analysis of risk factors for in-hospital myocardial infarction after total joint arthroplasty. Int Orthop. 2015 Apr;39(4):777-86. doi: 10.1007/s00264-014-2502-z. - Keshkar S, Kumar R, Bharti BB. (2014) Epidemiology and impact of early rehabilitation of spinal trauma after the 2005 earthquake in Kashmir, India. Int Orthop. 2014 Oct;38(10):2143-7. doi: 10.1007/s00264-014-2431-x. Authors' response Many thanks for your comments. The suggested references however interesting, does not seem to cater to this population of interest. The suggested first article focusses on myocardial complications in those undergoing arthroplasty. The second suggested article main emphasis is on spinal trauma and does not refer to the HIV population. Thus we have decided not to go forth inserting these references and no further actions were taken. We do think that these articles are useful and may be included in a future study. Reviewer #2: This is a nice review paper suggesting the well-known fact that there is a place in HIV patients to surgical fixation of fractures. However the authors should: 1) Explain in the "Introduction" and in the "Discussion" the meaning of ART and the new development in this mode of treatment and describe the change in morbidity and mortality in HIV patients" in the last few years and the relation of this change to their findings Authors' response Many thanks for your comments. We agree that a further explanation on ART should be included to the reader. This was included in the "Introduction." Clarification on the morbidity and mortality reduction since the introduction of ART in HIV infected patients was also included. Regarding discussing the new developments in ART, this is a whole topic in itself and beyond the scope of this review. However, we are currently finalising a similar systematic review focusing on the effect of ART on bone metabolism and fracture healing which we will submit for consideration for publication in your journal soon. Authors' action

	The following changes have been made; The introduction of Anti-Retroviral Therapy (ART) in 1997 altered the course and nature of patients infected with HIV by increasing the duration of asymptomatic infection and increasing life expectancy [2,3]. ART is a combination of medication given to those affected with the disease. This suppresses the viral load and improves the patient immunological status[4]. A 50% reduction in morbidity and mortality has been reported in those with a CD4 T-cell count of >500cells/mm3 and have been started on ART promptly [5,6]. However, despite near normal life expectancy, there is little evidence to advise the surgeon and patient about the effect of long-term immunosuppression in HIV-positive patients and implant usage in orthopaedic surgery [7]. 2) Add the effect of ART to the "conclusions" and the "Abstract" Authors' response We believe that the effect of ART is an important but as stated earlier is beyond the focus of this current review. We have included the following changes but it will be explored in a future paper but in summary very little research has been undertaken into the unique field. Thus necessary alterations to the document have been made. Authors' action The following changes have been made to the abstract and the conclusion. Abstract The effect of anti-retroviral therapy is unclear and this should be further researched. However, based on the limited evidence, caution should be taken in the management of open fractures due to the potentially increased infection risk. Conclusion The effect of ART on bone healing is uncertain and has not been sufficiently investigated. There are areas where more research is necessary, in particular the effect of HIV and ART on wound infection rate after open fractures, as well as the impact of HIV and ART on fracture union. 3) Arrange "References" according to the Journal format Authors' response The authors identified that there was an error in the referencing and this was sorted through out the document. All journal names were ensured that standard journal abbreviations were used in place of full journal names. All issue numbers of journal articles were removed. Authors' action Few examples of the references; 7. Chen LF, Hoy J, Lewin SR (2007) Ten years of highly active antiretroviral therapy for HIV infection. Med J Aust 186:146-151 8. Hankemeier S, Grassel S, Plenz G, Spiegel HU, Bruckner P, Probst A (2001) Alteration of fracture stability influences chondrogenesis, osteogenesis and immigration of macrophages. J Orthop Res 19:531-538. doi:10.1016/s0736-0266(00)00044-9 9. Hauser CJ, Zhou X, Joshi P, Cuchens MA, Kregor P, Devidas M, Kennedy RJ, Poole GV, Hughes JL (1997) The immune microenvironment of human fracture/soft-tissue hematomas and its relationship to systemic immunity. J Trauma 42:895-903; 10. Bongiovanni M, Tincati C (2006) Bone diseases associated with human immunodeficiency virus infection: pathogenesis, risk factors and clinical management. Curr Mol Med 6:395-400

Fracture management in HIV positive individuals: A systematic review

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Abstract

Purpose: Human immunodeficiency virus (HIV) infection could potentially play an important role in the management of fractures as they have been shown to affect fracture healing and the post-operative risk of implant sepsis.

Methods: A systematic review of the relevant literature was performed on PubMed and Scopus databases. Twenty-six studies were identified, critiqued and analysed accordingly. No randomised controlled trials were identified.

Results: HIV positivity was not shown to influence an individual's risk of early wound infection in operatively managed closed fractures. The rate of pin track infection in open injuries managed with external fixators was low. However, in open injuries managed with internal fixation, early wound infection rates were increased in the HIV-positive population compared to HIV-negative individuals. Regarding late implant infection, in closed fractures there appeared to be no increased risk of infection but there is limited evidence for open injuries. Additionally, further evidence is needed to establish if the rate of union in both open and closed fractures are influenced by HIV status.

Conclusion: Overall, no evidence was found to suggest that surgical management of fractures in the HIV population should be avoided, and fixation of closed fractures in the HIV population appeared to be safe. The effect of anti-retroviral therapy is unclear and this should be further researched. However, based on the limited evidence, caution should be taken in the management of open fractures due to the potentially increased infection risk. The impact of anti-retroviral therapy on the outcomes of surgery needs further evaluation.

Keywords: HIV; ART; Fracture; infection; union

1. Introduction

Worldwide approximately 35.3 million people are Human Immunodeficiency Virus (HIV) positive, with the highest prevalence seen in Sub-Saharan Africa [1]. The introduction of Anti-Retroviral Therapy (ART) in 1997 altered the course and nature of patients infected with HIV by increasing the duration of asymptomatic infection and increasing life expectancy [2,3]. ART is a combination of medication given to those affected with the disease. This suppresses the viral load and improves the patient immunological status [4]. A 50% reduction in morbidity and mortality has been reported in those with a CD4 T-cell count of >500cells/mm^3 and have been started on ART promptly [5,6]. However, despite near normal life expectancy, there is little evidence to advise the surgeon and patient about the effect of long-term immunosuppression in HIV-positive patients and implant usage in orthopaedic surgery [7].

HIV principally affects a patient's immunological status by reducing the host CD4 T-cell count, resulting in an increase in the risk of a patient developing opportunistic infections. HIV has also been shown to affect other chemical mediators, including interleukins 1 and 6 and tumour necrosis factor, which have been shown to play a role in the fracture repair process [8-10].

HIV and ART have both been shown to reduce bone mineral density (BMD), bone mineralization and bone turnover [11-15]. In the general population, it has been postulated that a reduced BMD is associated with a reduced speed of fracture healing [16]. If this relationship were to hold true in the context of HIV, then positive individuals would not only be at an increased risk of fragility fracture, but also of subsequent delayed fracture healing and failure of fracture fixation.

A major factor known to affect fracture healing is local blood flow to the site of the injury. It is now well established that any stage of HIV infection is associated with osteonecrosis, due to interruption in osseous blood supply, although no mechanism for this has been shown [17-19]. ART has also been reported to contribute to this pathology [18]. Conditions that jeopardize arterial flow to the site of primary bone healing are associated with higher rates of delayed fracture healing and non-union [20-22].

A small number of studies have investigated the role of HIV in the fracture healing process. These have suggested that HIV and/or ART are associated with delayed fracture healing and may result in non-union [23,24]. The molecular and cellular mechanisms driving this remain unclear and the true effect of HIV and ART on bone healing is very poorly understood.

The aim of this study is to undertake a systematic review of the outcomes of operative treatment of fractures in HIV positive individuals. A formal meta-analysis could not be carried out due to the significant variability in the methodology and outcome measures in each study.

2. Methods

The search strategy was formulated with key-concepts identified using the Population, Intervention, Comparator and Outcome (PICO) process[25] to identify search-terms. These were exploded to include synonyms, alternative spellings and related terms. MeSH (Medical Subject Headings) were combined using a Boolean technique to improve the search [26,27]. Specific terms and limitations were subsequently introduced and combined to refine the search [28].

Both PubMed and Scopus databases were searched as no single database covers all the resources within a given field [29].

The last search was carried out on 24th March 2016. The eligibility criteria are listed in Table 1.

Backward referencing of eligible studies and existing reviews were carried out to increase the number of relevant studies. Abstracts of relevant orthopaedic journals and HIV/Acquired Immune Deficiency Syndrome (AIDS) conferences were included to increase the number of studies.

The systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance [30]. The process of the literature search is summarised in Figure 1. The search yielded a total of 26 studies, which were included in this systematic review. Studies that met the inclusion criteria were summarised onto a spreadsheet to extract data. The summary consisted of study results, methods, limitations and treatment centres so that readers may interpret the resource context and compare outcomes between centres.

3. Results

3.1 Early Infection

3.1.1. Closed fractures

There were 7 studies that investigated early wound infection and/or early implant sepsis in closed fractures managed with open reduction and internal fixation (Table 2). The time period that was used to assess infection varied between studies. In this systematic review, early wound infection was defined as an ASEPSIS[31] score >10 as this would suggest a disturbance of wound healing [31]. This same definition of an ASEPSIS score of greater than 10 was used by the Malawi group [31]. However, the definition used in the other studies was not consistent [32,24,33-37].

In a retrospective single blind study, Paiement et al[32] from San Francisco, USA, reported a zero wound infection rate for closed fractures for HIV positive patients (n=14) whereas in the HIV negative control group (n=446) it was 4%. As ART status was not mentioned, and as this study was carried out in the pre-ART era it was assumed that none of the patients were on ART.

Similar results were reported by Harrison et al[24], from Malawi, in a prospective single blind study. They reported the results of a larger study population of 28 that were also ART naïve and a control HIV-negative group of 108. Wound infection rates were 4% and 6% respectively, which were not statistically significant. It was noted that 35% (n= 38) of the HIV population had CD4 counts <200.

Bahebeck et al[34] from Cameroon, demonstrated an infection rate of 5% (n=74) in his HIV-positive study group compared to 1% (n=572) in the HIV-negative control group. This study prospectively analysed a cohort of patients with closed injuries that underwent surgery for fresh fractures, non-union, malunion, aseptic necrosis, and osteoarthritis. Fresh fracture was the most common indication. Prior to surgery, 5% were on ART, which increased to 59% (n=74) at follow-up. Forty-four patients had a CD4 count <500 and were considered immunodeficient. They were started on ART at the time of injury.

In the largest prospective single blind study, researchers from Malawi reported the outcome of 118 HIV-positive cases and 418 controls [36]. They reported wound infection rates of 4% in HIV-positive patients and 6% in the control group, which was not statistically significant different. In this study 5% of the 118 HIV-positive patients were initially on ART, which later increased to 16% post-operatively.

Similar overall rates were reported by Nawale et al[33] 2006 from Pune, India in a retrospective analysis of 35 patients, in both ART naïve HIV-positive and control groups. Their wound infection rates were 6% (n=35) and 4%(n=35) respectively.

The most recent study carried out by Hao et al[37] (Denver, USA), did not use the ASEPSIS score to define infection. Instead the surgical site infection (SSI) was used (Centre for disease Control/ National Healthcare Safety Network). In 24 patients with HIV, majority of patients were taking ART (92%,n=22) at the time of injury. One patient developed a SSI, resulting in a 4% rate of early wound infection in this cohort.

Not all researchers have found low rates of infection. Abalo et al[35] (Togo) reviewed HIV-positive patients with 28 closed fractures managed with open reduction and internal fixation. They reported an infection rate of 29%. Prior to surgery, 35% of the patients were on ART. No control group was reported.

3.1 2. Open fractures

- Wound infection

Fourteen studies examined wound infection in HIV-positive patients managed operatively after open fractures (Table 3). These studies were extremely heterogeneous in design. Varying definitions of wound infection were used and in some studies the methods of determining wound infection rates were not stated. An array of fixation methods and injuries were included and commonly the grade of open injury was not defined. When external fixators were used to manage injuries, it was not always clear to determine if wound infection rates were referring to pin track infections or infection around the fracture site. Furthermore, the vast majority of studies were retrospective and patients were followed up for different lengths of time.

Howard et al[38] from Empangeni, South Africa studied open tibial fractures and reported an early wound infection in 11%(n=28) of their HIV-positive group; in comparison to the control group, which had a rate of 20%(n=57). Among the HIV-positive cohort the mean CD4 count was 432 and only 11% (n=28) patients were on ART. In a prospective analysis by Aird et al[39] from the same research group, 35 ART naïve patients underwent various methods of internal and external fixation following open injuries. The rate of early wound infection in this group was 15% (n=33), whereas the HIV-negative group had a 22%(n=86) infection rate, giving a risk ratio of 0.69. It is important to note that Aird et al results showed variation infection rates among the Gustilo-Anderson grades, with higher rates of infection in grade-I and-II, compared to III. Similar wound infection rates of 5%(n=39) were reported by Nawale et al[33] and other smaller cohorts have echoed these results. [40,41]

Conversely, Bates et al[36] from Malawi studied 21 HIV-positive patients in a prospective single blind cohort study who had undergone a number of different forbms of fixation, including K-wire, screws, plates and nails. The infection rate was 33% in their study population, while the HIV-negative control group had an infection rate of 15% (n=81). Only 5%(n=21) of their study cohort were on ART preoperatively, which increased to 16% post-operatively.

The majority of the smaller studies (i.e. < 20 patients) demonstrated high rates of infection in patients managed operatively following open fractures.[24,32,35,33,42,43] However caution needs to be used when interpreting their results due to the small numbers.

- Pin track infection

Four studies focussed on analysing the incidence of pin track infections in HIV-positive patients managed with external fixators following open fractures (Table 3). They all classified the pin track infections using the Checketts[44] scoring system. Howard et al[38] (Empangeni, South Africa) studied 17 HIV-positive patients and found severe (grade-V or -VI) pin track infection rate of 18%, whereas the infection rate for the HIV-negative control group of 40 patients had an infection rate of 13%. In the retrospective study by Ferreira et al[45] (Pietermaritzburg, South Africa) pin track infections of a Checketts score >II were studied. The pin track infection rate was 20% in their HIV-positive study population of 40 patients (63% of whom were started on ART post operatively). They reported a similar infection rate of 21% in a larger HIV-negative cohort (n=168). A third group of participants of unknown HIV status HIV had pin track infection rate of 24%. There was no statistically significant difference for incidence or severity between the three groups.
Norrish et al[46] (Malawi) studied 15 HIV-positive patients stabilised with external fixation, who were not on ART. This group had a pin track infection rate (Checketts score>II) of 60% compared to 20% in the HIV-negative control group of 35 patients. Only one patient needed a surgical intervention. Harrison et al 2004[47] observed a 75% rates of pin track infection in 7 cases while in 21 controls in their study had infection rates of 19%.

3.2 Long-term outcomes

3.2.1 Late implant sepsis

There were 5 studies that examined late implant sepsis in closed and open fractures (Table 4). We defined late implant sepsis as deep infection, which became evident 6 or more months after index surgery.

In prospective studies, Harrison et al 2004[48] (n= 26) and Graham et al[49] (n=103) (both Malawi) reported that there were no late implant infections for closed fractures; the mean follow up in these studies was 12 and 27 months respectively. No patient was on ART in the Harrison study and treatment rates was 8% pre-operatively and 27 % post-operatively in the Graham study.

In a prospective study carried out by Keetse et al[50] (Empangeni, South Africa) 12-month late implant sepsis rates were 3% for both HIV-negative (n=120) and HIV-positive (n=40) groups. Brijlall[51] (Durban, South Africa) found that 18 of 21 late implant infections were seropositive for HIV; patients presented a mean of 24 months (no range given) after index surgery. Neither of the studies stated the definition of late implant sepsis which could have had a major bearing on the recorded rates of infection.

In terms of late sepsis after open fractures, Graham et al[49] did not find any cases in twelve patients. Phaff et al [52] (Empangeni, South Africa) had a late implant sepsis rate of 8% in both the HIV-positive study population, and the HIV-negative cohort.

3.2.2 Non-union

In the non-union studies, a clear definition of the method for determining fracture union either radiologically or clinically was not documented, making accurate interpretation of the results difficult. There was also a large variation in duration of follow up, showing the lack of consistency of these studies. Defining union is challenging due to the lack of standardised assessment methods and even though radiological evaluation was carried out in most studies, no validated tool was used to assess union. For this review, a delayed union was defined as a fracture that was not healed at 6 months and a non-union was defined as a fracture that had not healed at 12 months. Clinically, union was considered to be present if there was return of function and weight bearing and a pain free range of motion, whereas for radiographic union 3 out of the 4 cortices on anterior-posterior and lateral X-rays had to be bridged.

- Non-union in closed fractures

Eight authors studied non-union in closed fractures, with a mix of prospective[48,50,53] and retrospective studies [35,54]. (Table 5)

The rates of non-union were 0% in 26 HIV-positive ART naïve patients that were clinically and radiologically evaluated in Malawi[48] and 5% in 95[53], 6% of whom were on ART; Keetse et al[50] (South Africa) looked at 40 closed femoral fractures that had undergone intramedullary nailing, however the method of evaluation of non-union was not described. Only one patient of the study group was on ART at the time of follow-up. None of the 40 patients developed non-union, whereas in the HIV-negative control group (n=120), had a rate of non-union of 2%.

Abalo et al[35] did not describe their definition of non-union, but reported rates of 11%(n=4) in an HIV-positive group of 36 patients. Cummins et al[54], in their retrospective study, also failed to give their definition of non-union, but reported that 3 of the 4 HIV-positive patients had non-union. Hao et al[37] followed a cohort of 24 HIV positive patients with closed fractures, none of whom developed non-union even though 92% of the patients were on ART.

Babruam[42] (Durban, South Africa) followed up 11 closed fractures in his study group of ART naïve patients that underwent intramedullary fixation and showed that all had united by four months. Brijlall[51] (Durban, South Africa) looked at an ART naïve cohort of 18 patients with infected implants postoperatively that presented late and found a rate of non-union of 11%. Neither Babruam[42] nor Brijlall[51] mentioned the method of evaluation of non-union.

- Non-union in open fractures

Six authors looked at non-union in open fractures. Aird et al[55] (Empangeni, South Africa) reported rates of non-union of 15%(n=33) for HIV-positive group and 4%(n=100) in the HIV-negative control group. However the method of evaluation, length of follow-up, grade of open fracture and energy of the initial injury were not clearly recorded. Furthermore, risk factors for non-union such as diabetes and smoking were not recorded.

In the prospective analysis of 13 individuals by Phaff et al[52] from the same study group as Aird, the rate of non-union was 8%(n=1). There was 1 patient who was on ART at the time of follow-up, who did not develop a non-union. In this study, which had a 39 month follow up, the rate of non-union in the HIV-negative control group was 0%(n=24). Participants underwent procedures that included intramedullary nails, plates, screws and tension band wiring. Union was assessed both clinically and radiographically in this study.

A retrospective study by Nawale[56] on 39 patients, not on ART, demonstrated rates of non-union of 10%. In the 5 patients Gardner et al[53] described a non-union rate of 20%. These three authors assessed patients for non-union on radiological imaging.

Prospective single blind cohort studies by Harrison et al[47] in 2004 and Babruam[42] followed patients up for less than 12 months, hence not fulfilling our criterion of non-union. Harrison et al[47] in 2004 followed their patients up for 6 months using clinical evaluations and radiographs. They reported a 43%(n=3) rate of delayed union in a 7 patient study group. Babruam[42] followed three patients who were HIV-positive for 4 months and reported that 1 patient (33%) did not show fracture union at the end of follow up, whereas the 2 HIV-negative patients had full fracture union.

Discussion

There have been a number of well-designed studies with appropriate length of follow up and number of patients that have evaluated early infection in closed fractures, demonstrating no increased risk of infection in patients with HIV [34,33,36].

In the pin track infections, all studies showed little difference between the HIV-positive and HIV-negative population, although the overall numbers of patients looked at were relatively small [44].

Mixed results have been reported for early wound infection rates in HIV patients with open fractures. Aird et al documented the largest study with lower rates of wound infection in the HIV-positive patients compared to HIV-negative control, but had variation among the Gustilo-Anderson grades. Patients with a grade-I Gustilo-Anderson had a delay in debridement in their study, which could account for the higher rates of infection observed in the grade-I open fractures. Excluding Howard's study, all the other studies reported an increased risk in the HIV-positive patients following open fractures. The varying quality of the studies reported so far make it difficult to draw clear conclusions, and more well designed and standardised studies including Gustilo-Anderson grading are needed.

The studies reviewed reported low rates of late implant sepsis in the HIV positive patients with closed fractures. In open fractures, there was too little data on late implant infection to draw valid conclusions

In all of the studies evaluated there was a lack of a clear definition of non-union to allow consistent evaluation between the studies. Fracture union is dependent on a huge number of different variables.[57,58]. All the studies evaluated were of poor study design, with no fixed definition of union and none used a validated radiological scoring system for bone union, such as the RUST Score [59,60]. Therefore, it is difficult to draw any valid conclusions from the studies reviewed.

Previous basic science research has suggested that HIV infection may associated with delayed and nonunion of fractures [23]. Researchers have hypothesized that altered cytokine environment arising from HIV infection may modify the inflammatory response which subsequently triggers the process of bone healing. There is increasing evidence to suggest that HIV seropositivity alone affects bone turnover, and in particular, may inhibit bone formation, which could contribute to issues with union. Furthermore, reports of osteonecrosis in HIV-positive patients without other risk factors poses the question as to whether HIV may compromise the reliability of the blood supply required for fracture healing [23].

Despite this fact, the studies evaluated suggest that non-union in closed fractures may not be a major concern in the HIV-positive individual. However, there is a need for further studies to be undertaken, using validated and accurate primary outcomes measures for bone union, in order to draw any valid conclusions. In open fractures there is also insufficient evidence to comment on bone union rates.

Most studies have not included enough patients on ART to draw meaningful conclusions. There has been an association shown between issues of non-union and the use of ART [23]. However, the multiple sources of heterogeneity such as duration of treatment, different drug regimens and differing degrees of immunosuppression

make it difficult to truly assess the effect. ART might also be expected to improve wound infection rates after open fractures and to reduce late implant sepsis in HIV-positive individuals, but current data lacks power to enable any such conclusions to be drawn.

The two largest surgeon study groups were from Africa. Hospital conditions and access to ART is substantially different to that of high-income countries. Caution should therefore be applied before direct extrapolation of published results to high-income settings.

Our study inclusion criteria ensured that all available literature was analysed, including abstracts that were not published as full papers, resulting in some loss of detail relating to study design and definitions. Other limitations were that any articles that were not in the English language were excluded.

It should be noted that supervision of this review came from the Harrison study group in Malawi, which could have been a potential source for bias. The first author and study selector made no reference to the principal researchers whilst searching and selecting studies so as to offset this possible bias.

Conclusions

Our study confirms that the surgical management of fractures in the HIV-positive groups should not be avoided. The outlook in the closed fractures is very encouraging, as it appears comparable to results obtained in HIV negative patients with equivalent injuries. The effect of ART on bone healing is uncertain and has not been sufficiently investigated. There are areas where more research is necessary, in particular the effect of HIV and ART on wound infection rate after open fractures, as well as the impact of HIV and ART on fracture union.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: No funds were received to undertake or relating to this study.

Ethical approval: Ethical approval was not required for this study design.

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Table 1 Inclusion and exclusion criteria

Type of criteria	Description	Rationale for criterion
Inclusion Criteria	Short or long terms patient outcomes or both post-operative management of fractures in HIV or AIDS (acquired immunodeficiency syndrome).	As per research question.
	Where indication for surgery were not fresh fractures, such as malunion, revision surgery, arthrodesis and arthroplasty were included as long as the majority of the procedures were fracture fixations.	This is to maximise the includible literature.
	Where multiple articles from the same study have been published more than once, only the single best study article was chosen unless subsequent publications included new data	
	Studies produced in the last 25 years.	
Exclusion Criteria	If spinal surgery/ maxillofacial surgery/ arthroplasty were the only focus of the study.	As per research question.
	No numerical data presented in the HIV positive category.	This is required to make a comparison of results among studies.
	If the early complications were not categorised into open and closed fractures.	This categorisation provides sufficient information for the results to be applicable to certain patient groups.
	Case reports	Epidemiological evidence carried forth by case reports are very minimal.
	Languages other than English.	Obtaining translations solely for this review was not financially feasible.

Table 2

Table 2 Early infection in closed fractures

Author	Year	Study type	Geographical location	Follow up period (months)	Patients on HAART prior to study	Patients on HAART at follow up	Definition of early infection	Outcome- Wound infection		HIV staging categories	Statistical analysis	Standard methods of evaluation	Limitations	Notes
								Study	Control					
G.D. Paiement [27]	1994	RSB	USA (San Francisco)	6.5	0/14 [0%}*	0/14 [0%]*	30 days	0/14 [0%]	14/446 [4%]	-	P=0.035, Chi-square in HIV positive group and wound infection	CDC definition	Retrospective	*No mention if patient were on HAART therefore assumed as not on HAART
W.J. Harrison [19]	2002	PSB	Africa (Malawi)	3	0/28 [0%]	0/28 [0%]	3 months	1/28 [4%]	6/108 [6%]	WHO staging, Stage 0= 2[80%], stage 1=3[8%], stage 2=2[5%], stage 3=2[5%] not known= 1[2%]; CD4 cell counts >500= 16%, 200-500= 49%, <200=35%	P value for closed fractures between HIV positive vs HIV negative =0.396. Not significant.	ASEPSIS wound score >10.	-	Contained a mix of patients with open and closed fractures
S. Nawale [28]	2006	R	Asia (India)	N/M	0/35 [0%]	0/35 [0%]	N/M	3/35 [9%]	2/35 [6%]	CD4 counts were between250-500. Values not mentioned.	NM	ASEPSIS wound score. Value not mentioned.	Retrospective. Not blind.	Follow up period not defined.
J. Bahebeck [29]	2008	P	Africa (Cameroon)	3	3/74 [5%]	44/74 [59%]	3 months	4/74 [5%]	3/572 [1%]	CD4 > 500= 30[41%], <500= 44[60%]	Fisher's exact test significant if <0.05, value =0.87	N/M	Not blinded,no standard use of scores such as ASEPSIS to measure infection.	Mixed cohort of patients. Majority were fresh fractures
A. Abalo [30]	2010	R	Africa (Togo)	27	16/36 [44%] ▲	16/36 [44%] ▲	N/M	8/28 [29%]	-	CD4>500= 21[58%], 200-500=12[33%], <200=3[8%] infection rates higher in symptomatic	P value <0.05 sig P for CD4 counts >2 = 0.041	N/M	No control. Retrospective. Not blinded. NO standard methods of ASEPSIS score used to measure infection.	▲ HAART assumed to be prior to injury.
J. Bates [31]	2012	PSB	Africa (Malawi)	1.5	7/139 [5%]	22/139 [16%]	6 weeks	5/118 [4%]	25/418 [6%]	CD4>500= 27[22%], 500-200= 69[56%], >500=28[23%] no relationship between ASEPSIS and CD4 count	P value <0.05 significant, HIV positive open vs HIV negative p=0.064. Not significant	ASEPSIS wound score >10.	Follow up of only 6 weeks	
J. Hao [32]	2015	P	USA (Denver)	12	22/24[92 %]	22/24[92%]	3 months	1/24 [4%]	-	CD4>500 =6[28%], 200-500=10[48%], <200=5[24%]	N/M	SSI-CDC/NHSN classification	High loss to follow-up. No control. Small sample size. Not blinded. Abstract.	-

Key: P- Prospective study; PSB- Prospective single blind study; R- retrospective study; RSB- Retrospective single blind study
N/M- not mentioned

Table 3

Table 3 Wound infection and open fractures (fracture management inclusive of internal fixation and external fixation)

Author	Year	Study type	Geographical location	Follow up period/months	Number of patients HAART prior to study	Number of patients on HAART at follow up	Definition of early infection	Outcome				HIV staging categories	Statistical analysis	Standard methods of evaluation	Limitations	Notes
								Wound infection		Pin track infection						
								Study	Control	Study	Control					
G.D. Paiement [27]	1994	RSB	USA (San Francisco)	6.5	-	0/11 [0%]*	30 days	4/11 [36%]	10/118 [9%]	-	-	-	P=0.035, Chi-square	CDC definition	Retrospective	*No mention if patient were on HAART therefore assumed as not on HAART
E.D. O'Brien [38]	1994	R	USA (New York)	Range 6-24	-	0/4 [0%]*	Range 6-24 months	4/4 [100%]	1/11 [9%]	-	-	-	-	-	Retrospective. Small study group. Abstract.	Follow up period not defined. *No mention if patient were on HAART therefore assumed as not on HAART
W.J. Harrison [19]	2002	PSB	Africa (Malawi)	3	0/12 [0%]	0/12 [0%]	3 months	5/12 [42%]	3/27 [11%]	-	-	WHO staging, stage 0= 2[80%], stage 1=3[8%], stage 2=2[5%], stage 3=2[5%] not known= 1[2%]; CD4 cell counts >500= 16%, 200-500= 49%, <200=35%	P value for open #s HIV positive versus negative =0.084	ASEPSIS wound score >10.	-	Contained a mix of patients with open and closed fractures.
W.J. Harrison [42]	2004	PSB	Africa (Malawi)	6	0/7 [0%]	0/7 [0%]	3 months	-	-	5/7 [71%]	4/21 [19%]	WHO staging- 0=4[57%], 1=1[14%], 2=2[29%] CD4 count <200= 2 [29%], 200-500= 2[29%], >500=[14%] unknown 2[29%]	P value for infection= 0.02 was significant	Pin track- Checketts	Small study population	
F.F. Birkholtz [35]	2005	P	Africa (South Africa)	N/M	0/16 [0%]*	0/16 [0%]*	N/M	0/3 [0%]	5/16 [31%]	-	-	N/M	N/M	N/M	Very small study population. Not blinded. Abstract. No standard method of measuring outcome such as ASEPSIS	*No mention if patient were on HAART therefore assumed as not on HAART

A. Baburam [37]	2005	PSB	Africa (South Africa)	4	0/3[0%] *	0/3 [0%]*	4 months	1/3 [33%]	0/2 [0%]	-	-	N/M	N/M	All fractures GA grade-II	Abstract. Follow up only 4 months, which is not sufficient to measure long-term outcomes. No standard method of measuring outcome such as ASEPSIS	Follow up period was mentioned but assumed to be 4 months according to what is mentioned in abstract. *No mention if patient were on HAART therefore assumed as not on HAART
A. Baburam [36]	2005	PSB	Africa (South Africa)	Mean 7.3 (range1-14)	0/10 [0%]	0/10 [0%]*	7.3 (range1-14)	1/10 [10%] GA grading I-0/1, II- 0/3, IIIa-1/3, IIIb-0/3	1/8 [13%] GA grading II-0/5, IIIa-0/1, IIIb-1/2	-	-	N/M	P=0.641 not statistically significant. P value given for infection rate in HIV positive versus HIV negative	N/M	Abstract. No standard method of measuring infection e.g. ASEPSIS score. Distribution of open fractures not evenly distributed in HIV positive and HIV negative groups.	*No mention if patient were on HAART therefore assumed as not on HAART
S. Nawale [28]	2006	R	Asia (India)	N/M	0/14 [0%]	0/14 [0%]	N/M	8/14 [57%]	3/14 [21%]	-	-	CD4 counts were between 250-500. Values not mentioned.	NM	ASEPSIS wound score. Values not mentioned.	Retrospective. Not blind.	Follow up period not defined.
S. Nawale [51]	2007	R	Asia (India)	12	0/39 [0%]*	0/39 [0%]*	1 year	2/39 [5%]	-	-	-	N/M	N/M	N/M	No control. Retrospective. Not blinded. Abstract. No standard methods to measure outcomes such as ASEPSIS.	*No mention if patient were on HAART therefore assumed as not on HAART
A.R. Norrish [41]	2007	PSB	Africa (Malawi)	2	-	0/15 [0%]*	2 months	-	-	9/15 [60%] Checketts II-7, III-1, IV-1	7/35 [20%] Checketts II-6, III-1	N/M	P value <0.05 significant, P= 0.01 => significant but P=0.07 when mean worst score / no of pin weeks=> not significant,	For pin track infection Checketts.	-	Patients were followed up as long they had an External fixator in situ. Where the mean time was 2 months. *No mention if patient were on HAART therefore assumed as not on HAART
A. Abalo [30]	2010	R	Africa (Togo)	27	16/36 [44%] ▲	16/36 [44%] ▲	27 months	6/8 [75%]	-	-	-	CD4>500= 21[58%], 200-500=12[33%], <200=3[8%] infection rates higher in symptomatic	P value <0.05 sig P for CD4 counts >2 = 0.041	N/M	No control. Retrospective. Not blinded. No standardised method of measuring outcomes e.g. ASEPSIS score.	▲ HAART assumed to be prior to injury

J. Aird [34]	2011	P	Africa (South Africa)	3	-	0/33 [0%]*	30 days	5/33 [15%] GA grade-abrasions-0/5, I-4/14, II-1/9, IIIa-0/3, IIIb-0/2	19/86 [22%] GA grade-abrasion-4/14, I-3/32, II-4/17, IIIa-3/12, IIIb-4/11	-	-	CD4 < 350 =15[58%], <100=0, 7 patients were not measured due to disease denial.	P value for infection= 0.49 in advanced HIV,- no statistical significance. Risk ration= 1.46[95% CI= 0.6-3.7; Risk of developing wound infection given HIV positivity, Risk ratio =0.69, 95% CI 0.3-1.7, P value 0.4. In HIV positive patients P value for abrasions =0.53, G.A. I= 018, G.A. II= 0.62 Risk ration (confidence interval) for G.A. I= 3.1(0.8-11), G.A. II=0.47(0.5-3.6). Values for other G.A. grading was not available. In Advanced HIV for G.A. I p value =0.02, risk ratio (confidence interval)= 6.33(1.8-23.0). Values for other G.A. grading were not available.	ASEPSIS wound score.	Not blinded.	*No mention if patient were on HAART therefore assumed as not on HAART
J. Bates [31]	2012	PSB	Africa (Malawi)	1.5	7/139 [5%]	22/139 [16%]	6 weeks	7/21 [33%]	12/81 [15%]	-	-	CD4>500= 27[22%], 500-200= 69[56%], >500=28[23%] no relationship between ASEPSIS and CD4 count	P value <0.05 significant, open HIV positive versus HIV negative p=0.064 not significant	ASEPSIS wound score >10.	Follow up of only 6 weeks	-
N.E. Howard [33]	2013	P	Africa (South Africa)	1-3	3/28 [11%] GA grading I-1, IIIa-1, IIIb-1	3/28 [11%] GA grading I-1, IIIa-1, IIIb-1	30 days	3/28 [11%] GA grading II-2/11	11/57 [20%] GA grading II-3/40, III-7/17	3/17 [18%] Only those with Checketts score >4	5/40 [13%] Only those with Checketts score >4	Mean CD4 = 432 (104-1190) no relationship between CD4 and ASEPSIS score. 4 had a CD4<350	P value for wound infection in HIV positive p= 0.32, RR=0.55, 95% CI = 0.17-1.8; P value for pin track=0.47, RR 1.62,95% CI 0.44 to 6.07, diff in wound infection rates between HIV positive and negative p=0.624 not statistically significant	ASEPSIS wound score >10, Checketts score of 4 for pin track infection.	Not randomised, not blind, insufficient grade III #s , need more data on lower CD 4 i.e. <350	-
N. Ferriera [40]	2014	R	Africa (South Africa)	5	0/40 [0%] ◆	25/40 [63%] ◆	23 weeks (range 6-104)	-	-	8/40 [20%] Checketts-II-6, III-1, IV-1	36/168 [21%] Checketts- II-26, III-6, IV-2, VI-2	Mean CD4=347.4, SD+/-162.4, range =82-682. No relationship between CD4 and infection	P=0.9 no difference	Checketts score.	Retrospective	◆ HAART assumed to be started post injury.

Key: P- Prospective study; PSB- Prospective single blind study; R- retrospective study; RSB- Retrospective single blind study
N/M- not mentioned

Table 4

Click here to download Table Table 4 Late implant sepsis inOpen and Closed fractures.docx

Table 4 Late implant sepsis in Open and Closed fractures

Author	Year	Study type	Geographical location	Follow-up period (months)	HAART prior to study % of patients	HAART (%) at follow-up	Outcome: Late implant sepsis				HIV staging categories	Statistical analysis	Limitations	Notes
							Closed		Open					
							Study	Control	Study	Control				
S. Brijlall [46]	2003	R	Africa (South Africa)	-	0/18 {0%}*	0/18 {0%}*	18◇	-	-	-	N/M	N/M	No control. No blinding. Follow up was not defined. Looked only at a cohort with infected implants.	Follow up time not defined. Looked only at patients who were infected. Hence all 18 patients had an implant sepsis. All cases that were looked at were also delayed presentation. ◇Only patients with late implant sepsis were included *No mention if patient were on HAART therefore assumed as not on HAART
W.J Harrison [43]	2004	P	Africa (Malawi)	12	0/26 [0%]*	0/26 [0%]*	0/26 [0%]	-	-	-	CD4 >500=7[27%], 200-500=8[31%], <200=9 [35%]	N/M	No control. No blinding. Follow up of only 12 months, not long enough for long-term outcomes. No standard method of scoring outcomes such as ASEPSIS	*No mention if patients were on HAART therefore assumed as not on HAART
M. Phaff [47]	2015	P	Africa (South Africa)	39 (mean)	0/13 [0%}	1/13 [0%}	-	-	1/13 [8%] GA grading abrasions 0/3, I-0/6, II- 0/3, IIIa- 0/0, IIIb=1/1	2/24 [8%] GA grading abrasions 0/5, I=1/11, II=0/3, IIIa- 0/3, IIIb=1/2	CD4>500=2 [15%] 200-500= 4 [31%] <200= 2[15%] Unknown=5[39 %]	Relative risk in open fractures = 0.92 (Confidence interval 0.092-9.2) P=1 (2 tailed Fischer exact test)	No control. Small sample size. Not blinded. No standard method of measuring outcome such as ASEPSIS. High rate of loss to follow-up	Only 1 patient was one HAART at follow up.
M.M. Keetse [45]	2014	P	Africa (South Africa)	12	12/40 [30%]	12/40 [30%]	1/40 [3%]	3/120 [3%]	-	-	CD4<350= in 7 patients	N/M	Not blinded. Abstract. Follow up for only 12months which is not enough for long term outcomes	Time HAART started not mentioned, so assumed to be prior to study.
S. Graham [44]	2015	PSB	Africa (Malawi)	27 (mean)	7/103 [6%]	25/103 [24%]	0/93 [0%]	-	0/12 [0%]	-	CD4 > 500= 21[23%] 200-500=58 [62%], <200=14[15%]	N/M	No control, treatment was not blinded/ randomised beyond initial early postoperative period, cohort of young patients mean age 42, majority CD>200 despite a low compliance with HAART	

Key: P- prospective study; PSB- Prospective single blind study; R- Retrospective study
N/M- Not mentioned

Table 5

Table 5 Non-union in Open and Closed fractures

Author	Year	Study type	Geographical location	Follow up period/ months	HAART prior to study % of patients	HAART (%) only in Study	Outcome				Categories	Statistical analysis	Standard methods of evaluation	Limitations	Notes
							Non-Union								
							Closed		Open						
							Study	Control	Study	Control					
S. Brijlall [46]	2003	R	Africa (South Africa)	N/M	0/18[0%]*	0/18[0%]*	2/18[11%] ▼	-	-	-	N/M	N/M	Only radiological assessment.	No control. No blinding. Follow up was not defined. Looked only at a cohort with infected implants.	Follow up time not defined. Looked only at patients who were infected. Hence all 18 patients had an implant sepsis. All cases that were looked at were also delayed presentation. *No mention if patient were on HAART therefore assumed as not on HAART ▼ Authors did not state if injuries were open or closed
W.J. Harrison [42]	2004	PSB	Africa (Malawi)	6	0/7[0%}	0/7[0%]	-	-	3/7 [43%]	1/21 [5%]	WHO staging; 0=4[57%], 1=1[14%], 2=2[29%], CD4 count; > 500= 2 [29%], 200-500= 2[29%], >5001[14%] unknown 2[29%]	P value for infection= 0.02 was significant, for union=0.059 not sig	Only clinical and radiological assessment.	Small study population	
W.J. Harrison [43]	2004	P	Africa (Malawi)	12	0/26[0%]*	0/26[0%]*	0/26[0%]	-	-	-	CD4 >500=7[27%], 200-500=8[31%], <200=9[35%]	-	Only clinical and radiological assessment.	No control. No blinding. Follow up of only 12 months, not long enough for long-term outcomes.	*No mention if patient were on HAART therefore assumed as not on HAART
A. Baburam [37]	2005	PSB	Africa (South Africa)	4	0/14[0%]*	0/14[0%]*	0/11[0%]	0/14[0%]	1/3[33%]	0/2[0%]	N/M	N/M	N/M	Abstract. Follow up only 4 months, which is not sufficient to measure long-term outcomes.	Follow up period was mentioned but assumed to be 4 months according to what is mentioned in abstract. *No mention if patient were on HAART therefore assumed as not on HAART
S. Nawale [51]	2007	R	Asia (India)	12	0/39[0%]*	0/39[0%]*	-	-	4/39 [10%]	-	N/M	N/M	Only clinical and radiological assessment.	No control. Retrospective. Not blinded. Abstract.	
A. Abalo [30]	2010	R	Africa (Togo)	27	16/36[44%] ▲	16/36[44%] ▲	4/36[11%] ▼	-	-	-	CD4>500= 21[58%], 200-500=12[33%], <200=3[8%]	P value <0.05 sig P for CD4 counts >2 = 0.041	-	No control. Retrospective. Not blinded.	▲ HAART assumed to be prior to injury ▼ Authors did not state if injuries were open or closed

											Infection rates higher in symptomatic				
R.O.E. Gardner [48]	2012	P	Africa (Malawi)	12	5/96[5%]	6/95[6%]	5/95[5%]	-	1/5[20%]	-	CD4 >500=[21%], 200-500=[64%], >500=[21%] no relation between CD4 and non-union	N/M	Only clinical and radiological assessment.	No control. Not blinded.	
J. Aird [50]	2012	P	Africa (South Africa)	N/M	0/33[0%]*	0/33[0%]*	-	-	5/33[15%]	4/100[4%]	N/M	P=0.04 for non-union, risk ratio=4	N/M	Not blinded. Abstract.	Follow up period not defined. *No mention if patient were on HAART therefore assumed as not on HAART
F. Cummins [49]	2014	R	Europe (Republic of Ireland)	25	12/17[71%]	13/17[76%	3/4 [75%]	-		-	CD4 > 500= 5, 200-500= 12, >500= 0	Correlation coefficient for complications and HAART use=-0.35 determination= 0.12. Non-significant	N/M	Small cohort, area of high social deprivation, heterogeneity of the surgical procedures in emergency surgery group, retrospective data collection, and short follow up for two of the surgeries.	
M.M. Keetse [45]	2014	P	Africa (South Africa)	12	12/40[3%] ■	12/40[3%]	0/40[0%]	2/120[2%]	-	-	7 patients withs CD4<350	N/M	N/M	Not blinded. Abstract. Follow up for only 12months which is not enough for long term outcomes	■ Time started not mentioned hence assumed it was prior to surgery
M. Phaff [47]	2015	P	Africa (South Africa)	39 (mean)			-	-	1/13 [8%] GA grading abrasions=0/3, I=0/6,II=0/3 IIIa=0/0 IIIb= 1/a	0/24 [0%] GA grading abrasions=0/5, I=0/11, II=0/3, IIIa=0/3, IIIb=0/2	CD4>500=2 [15%] 200-500= 4[31%] <200= 2 [15%] Unknown=5 [39%]	N/M	Only clinical and radiological assessment.	High loss to follow-up. No control. Small sample size. Not blinded.	Only 1 patient was on HAART at follow-up
J. Hao [32]	2015	P	USA (Denver)	12	22/24[92%]	22/24[92%]	1/24[4.2%]	-	-	-	CD4>500 =6/21, 200-500=10/21, <200=5/21	N/M	Only clinical and radiological assessment.	High loss to follow-up. No control. Small sample size. Not blinded. Abstract.	-

Key: P – Prospective study; PSB- Prospective single blind study; R- retrospective study
N/M- not mentioned

Figure 1 Click here to download Figure Fig 1- MeSH terms used.docx

Fig 1- MeSH terms

MeSH term 1	MeSH term 2	MeSH term 3
HIV	Fractures	Union
		Sepsis
	Wound infection	
	Implant sepsis	
	SSI	
	Surgical site infection	
	Early sepsis	
	Late sepsis	
	Pin track infection	
	Non-union	

Figure 2 Click here to download Figure Fig 2- Flow diagram (1).docx

Fig 2 - Flow diagram