TRIUMA

The effect of HIV on early wound healing in open fractures treated with internal and external fixation

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Historically, the treatment of open fractures has often depended on the grade of the wound, but more recent scoring systems and management algorithms have acknowledged the importance of host factors. Human immunodeficiency virus (HIV) is the most common cause of severe immunosuppression in many countries. There are 33 million people worldwide currently infected with HIV.

Patients with HIV disease have been found to have high rates of wound sepsis following the internal fixation of open fractures and high rates of pin-track sepsis in externally fixed fractures, but these studies have lacked statistical power. Laboratory-based studies have shown that HIV infects a variety of cells, including lymphocytes and macrophages. Once infected, these cells become dysfunctional and may undergo apoptosis. Subgroups of these cells are known to be important for initiating and regulating wound healing and in the immune response to bacterial infection.

The severity of disease can be assessed by the CD4 T-cell count in the blood. This study was undertaken in 2008 and 2009, when few patients were on highly active anti-retroviral therapy (HAART). Subsequent guidelines had suggested starting the therapy when CD4 counts fall below 200 cells/μl. Since 2009 the criteria for treatment with HAART have been broadened in South Africa, such that most patients with CD4 counts < 350 cells/μl are now on this regimen. The increased availability of this treatment has had a dramatic effect on the life expectancy of patients with HIV, although it remains an incurable disease owing to reservoirs of infection in cells such as macrophages.

The treatment of open fractures with internal fixation in certain situations is now considered the optimal method of treatment, despite serious complications such as infection and nonunion. There are many factors that influence the development of infection in the presence of metalwork. However, once infection has occurred, it remains difficult to treat and often requires removal of the metalwork and surgical debridement.

It is not currently known whether HIV is a significant risk factor in the development of a wound infection or nonunion in open fractures and it therefore remains difficult to choose the optimal method of treatment. This study aimed to investigate the null hypothesis that there is no association between HIV or advanced HIV disease (CD4 < 350 cells/μl) and wound infection in open fractures treated by internal fixation.
Patients and Methods
The study was carried out in the orthopaedic department of Ngwelezane Hospital, KwaZulu-Natal, South Africa in an area with a high incidence of trauma and some of the highest rates of HIV in the world.\textsuperscript{20} It was a prospective epidemiological observational study and included all adults admitted to the hospital who underwent internal or external fixation for open fractures (including significant abrasions over the fracture site) between May 2008 and March 2009. The study period was chosen to ensure a minimum follow-up of three months. Fractures with abrasions were included to match\textsuperscript{1} the inclusion criteria used in the Malawi study by Harrison et al.\textsuperscript{5}

Exclusion criteria were admission to ICU, mental illness, patients from out of the area, those unable to provide an address and contact number, and patients discharged to prison. This yielded 133 patients with 135 fractures, 33 of whom had HIV.

A power study based on previous work by Harrison et al\textsuperscript{5} suggested that 21 HIV-positive patients and 63 HIV-negative patients were required to allow statistically valid conclusions to be reached. This assumed a HIV-negative to positive patient ratio of 3:1 and identified a 4.2-fold increase in acute wound infection in the HIV-positive group. The numbers in our study satisfied this power calculation.

Patient management followed departmental protocols and was not affected by HIV status. This was assessed by retrospective review of patients notes after discharge. All patients received intravenous antibiotics, with flucloxacillin 1 g qds started on admission and continued for three days, with gentamicin 240 mg daily added for injuries below the knee. In cases where staged debridement was required, the antibiotics were continued until the wound was closed. The management of grade I\textsuperscript{21} fractures differed from the more severe grades of injury in that patients did not undergo emergency debridement. This protocol was based on the evidence of Yang and Eisler.\textsuperscript{22}

The outcome measure was wound infection within 30 days of fixation assessed using the ASEPSIS\textsuperscript{23} scoring system (Table I) because it had been used in a previous similar study\textsuperscript{1} and therefore facilitated valid comparisons.

### Statistical analysis
The binary nominal data were analysed using the chi-squared test. In cases where the expected value was < 5, Fisher's exact test was used. The Mann-Whitney test was used to assess differences between the ages of different groups. Tests were all two-tailed and a p-value was used to gauge significance, which was set at p < 0.05. This study was a prospective case-control study, and therefore risk ratios are given where appropriate. In the assessment of multiple potential risk factors, binary logistic regression was used.

### Results
The study included 133 patients (135 fractures) with a mean age of 33 years (17 to 83). The most common mechanism of injury was gunshot wounds, with motor and pedestrian vehicle accidents making up the majority of the remainder. A total of 43 fractures were in the tibia, 38 in the femur, 37 in the bones of the forearm, 14 in the humerus, and three in other sites in the body. Figures 1 and 2 show the distribution of grade of injury and method of fixation used within the cohort. Table II shows the demographic comparisons between HIV-positive and -negative patients and those who refused testing. Of the 33 patients who tested positive for HIV, 26 (79%) had a CD4 count recorded and 15 (58%) of these had advanced HIV (CD4 count < 350 cells/μl).\textsuperscript{24} No patient had a CD4 count < 100 cells/μl. There were seven patients who refused or failed to produce a CD4 count following a positive HIV test. This was due in some cases to disease denial from the patient, and in others to the requirement to have an identity number in order to get a CD4 count processed, which not all patients had or knew.

Table III shows that patients with HIV disease had a lower rate of wound infection than those without (15%...
and 22% respectively, but this finding lacks statistical significance (p = 0.4).

Table IV shows that patients with advanced HIV had a higher rate of infection than those without advanced HIV (both HIV-negative and -positive) (27% and 18%, respectively), and this finding also lacks statistical significance (p = 0.49).

Subgroup analysis was used to look at infection rates with and without HIV infection in different grades of wound, and this showed strong evidence of an association between advanced HIV and wound infection in grade I injuries (risk ratio = 6.33, p = 0.02) (Table V). According to the department protocol, patients with a grade I injury were not taken to theatre for urgent debridement, but were placed on daytime lists for urgent fixation, if required, whereas those with grade II and III injuries underwent emergency debridement and fixation. Occasionally a delay in presentation or delay in referral meant a long delay until debridement (Table VI). This shows that grade I injuries had, on average, a longer wait for debridement than the higher-grade injuries.

Logistic regression. Logistic regression analysis showed that the grade of wound and delay to debridement were the biggest risk factors for wound infection (Table VII). Neither HIV nor smoking was associated with an increased risk of wound infection when the other factors were taken into account.
account. However, HIV was a risk factor when the other factors had been accounted for, but this did not reach statistical significance (p = 0.31).

Comparison of the demographic data of the cohorts revealed several differences. Patients with HIV were more likely to be smokers (p = 0.028). Smoking is known to be a risk factor for nonunion,25 however, it is possible that patients with HIV are more likely to smoke because of increased risk-taking behaviour, and therefore smoking may not be an independent confounder. Although all patients were counselled about the need to stop smoking, few did. It was not possible to quantify accurately the numbers of cigarettes patients smoked. Financial constraints meant that most patients bought cigarettes one at a time, smoking more around pay day.

Discussion

Based on these results, there is no evidence to reject the null hypothesis that there is no association between HIV and risk of early wound infection in open fractures treated with fixation. The data show that the risk of infection was similar in both HIV-positive and -negative patients. This was unexpected, as previous studies had suggested a much higher risk of infection in HIV-positive patients.5,7 The risk (unadjusted for other factors) increased slightly in patients with advanced HIV, but the difference remained small and did not reach statistical significance (p = 0.49). Table VIII shows a comparison of the data presented in this study and previous studies regarding wound infection in open fractures.5,6,8,26

Our data differ significantly from other studies, in both numbers of patients and outcome. It has three times the number of HIV-positive patients of either of the previous studies,5,7 and is the only study not to show an increase in the risk of wound infection. Although all three studies are looking at the same outcome, the inclusion criteria vary significantly. Paiement et al7 investigated any procedure that required surgical debridement, whereas Harrison et al5 included many patients who were undergoing repeat operations for previously infected nonunions. The grades of fracture were not described the previous studies, and correlations with advanced HIV were not made.

Both subgroup and logistic regression analysis suggest that it is only patients with advanced HIV who may be at higher risk of infection. This should give surgeons confidence when treating patients with early HIV using either internal or external fixation, that their patients are not at higher risk of infection than the general population.

Subgroup analysis highlighted that patients with grade I fractures who were HIV-positive with a low CD4 count had a
higher risk of wound infection than HIV-negative patients. The observations recorded following the grade I fractures may be the result of their different management, resulting in delayed surgery and less extensive debridement, as well as a shorter course of antibiotics compared with the higher-grade injuries. This suggests that our management protocol for grade I open fractures requires modification so that they are treated more urgently and aggressively. We speculate that in the immunocompetent patient the relatively small inoculum from a grade I injury is adequately controlled by the immune response and antibiotic administration. In the immunodeficient patient the immune response is inadequate, and if the inoculum is left the bacteria proliferate, leading to a wound infection. This hypothesis needs to be tested with further studies.

Logistic regression analysis identified grade of wound as the most important risk factor for wound infection, followed by smoking and HIV-positivity.

Table V. Subgroup analysis by grade of injury (Gustilo-Anderson) for wound infection given human immunodeficiency virus (HIV) or advanced HIV infection

<table>
<thead>
<tr>
<th>HIV infection</th>
<th>Abrasions</th>
<th>I</th>
<th>II</th>
<th>Illa</th>
<th>Illb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>0/5 (0)</td>
<td>4/14 (29)</td>
<td>1/9 (11)</td>
<td>0/3 (0)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>Risk ratio of wound infection given HIV-positivity (95% CI)</td>
<td>NA</td>
<td>3.1 (0.8 to 11)</td>
<td>0.47 (0.5 to 3.6)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>p-value</td>
<td>0.53</td>
<td>0.18</td>
<td>0.62</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Advanced HIV</th>
<th>Abrasions</th>
<th>I</th>
<th>II</th>
<th>Illa</th>
<th>Illb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>0/2 (0)</td>
<td>4/8 (50)</td>
<td>0/1 (0)</td>
<td>0/2 (0)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>Risk ratio of wound infection given advanced HIV (95% CI)</td>
<td>NA</td>
<td>6.33 (1.8 to 23.0)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>p-value</td>
<td>NA</td>
<td>0.02</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* CI, confidence interval
† NA, not available
‡ Fisher’s exact test

Table VI. Average delay to surgery for the different grades of wound

<table>
<thead>
<tr>
<th>Grade</th>
<th>Delay to surgery/days (median, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
</tr>
<tr>
<td>I</td>
<td>3.5</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
</tr>
<tr>
<td>Illa</td>
<td>0.75</td>
</tr>
<tr>
<td>Illb</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* HIV, human immunodeficiency virus

Table VII. Logistic regression analysis of potential risk factors for wound infection

| Risk factor | Adjusted risk ratio for wound infection | p-value
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High-grade wound (II or III)</td>
<td>2.3</td>
<td>0.12</td>
</tr>
<tr>
<td>Delay greater than 24 h to debridement</td>
<td>1.7</td>
<td>0.31</td>
</tr>
<tr>
<td>Smoking</td>
<td>5</td>
<td>0.17</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>8</td>
<td>0.84</td>
</tr>
<tr>
<td>Advanced HIV</td>
<td>2</td>
<td>0.31</td>
</tr>
</tbody>
</table>

* HIV, human immunodeficiency virus
† based on separate analysis

Table VIII. Comparison of wound infection rates with those of previous studies

<table>
<thead>
<tr>
<th>Wound infection (number (%))</th>
<th>The relative risk (RR) of developing a wound infection given HIV-positivity (95% confidence interval)</th>
</tr>
</thead>
</table>
| Yes | No | RR | p-value
| Paiement et al | HIV-positive | 4 (31) | 9 (69) | 3.04 (1.1 to 8.5) |
|       | HIV-negative | 9 (10) | 80 (90) | p-value | 0.06 |
| Harrison et al | HIV-positive | 5 (42) | 7 (58) | 3.75 (1.1 to 13.2) |
|       | HIV-negative | 3 (11) | 24 (89) | p-value | 0.08 |
| Aird (present study) | HIV-positive | 5 (16) | 28 (88) | 0.69 (0.3 to 1.7) |
|       | HIV-negative | 19 (22) | 67 (78) | p-value | 0.4 |

* HIV, human immunodeficiency virus
† Fisher’s exact test
‡ chi-squared test
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by advanced HIV. This analysis lacked statistical power, although it has biological plausibility. There are many factors associated with advanced HIV that have been shown to be related to wound problems; these include hypoaalbuminemia,27 anaemia28 and concurrent infection.29 Further trials are required to identify whether these findings are significant in relation to wound infection. Many patients with advanced HIV are now receiving HAART and their CD4 counts often recover, although other cell types may remain severely impaired.30 Further studies are required to look at this population to identify whether they are at higher risk of wound infection following open fracture.

Internal fixation in open fractures in the HIV-positive population is frequently eschewed because of worries over infection. This is based on four previous trials and the personal experience and fears of the operating surgeon.5-8 In our series, with the notable exception of grade I fractures in the immunocompromised HIV-positive patient with a low CD4 count, wound infection rates in the HIV-positive and -negative patients were similar. We therefore believe that HIV should not be considered a contraindication to fracture fixation, although we acknowledge that our results may not correlate with patients with very low CD4 counts (< 100), as these were not seen on our cohort.

This study was a prospective observational cohort study with several limitations. The management of patients was not blinded, and this could have introduced bias, although we instituted protocols to try and ensure that management was not affected by HIV status. We then audited the notes to ensure that the protocols had been followed. Infection was measured using the ASEPSIS scoring system, which still had a degree of subjectivity in its use. Owing to the lack of blinding it is possible, despite all the precautions taken, that this subjectivity could have introduced bias.

This paper has not addressed the possibility of delayed infection in the HIV-positive patient; the potential for this problem needs to be considered when deciding on the best method of treatment of an open fracture. In this respect, we believe that external fixation should be considered for fractures in locations where it is recognised as an acceptable treatment method with similar results to internal fixation, for instance in open tibial fractures in HIV-positive patients, as the cost and morbidity of delayed infection may be avoided. The incidence of delayed infection in HIV-positive patients is the subject of an ongoing study by the author, the results of which may accurately guide initial treatment.

Supplementary material

A further opinion by Professor S. Hughes is available with the electronic version of this article on our website at www.jbjs.org.uk

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References


