

# Non-traumatic Bilateral Lower Limb Fractures in Human Immunodeficiency Virus Positive Individuals on Long-Term Antiretroviral Therapy: Two Case Reports and Literature Review

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## Learning Point of the Article:

Long-term use of ART drugs can lead to pathological fractures in these patients so optimal correction of metabolic abnormalities and multidisciplinary approach is necessary in treatment of such patients.

## Abstract

**Introduction:** It has been noticed that human immunodeficiency virus (HIV) infection and anti-retro viral (ART) therapy, both individually lead to bone metabolic disorders, and hence, such patients have an increased propensity for fractures following trivial trauma.

**Case Report:** We present two cases, first a 52-year-old female with the right hip pain and inability to walk since 1 week following trivial trauma and associated dull pain in the left hip since 2 months ago. Radiographs revealed a right intertrochanteric fracture and a left unicortical fracture at level of lesser-trochanter. The patient was managed with closed proximal femoral nailing bilaterally and subsequently mobilized. Second, a 70-year-old female with bilateral leg pain and swelling following trivial trauma since 3 days. Radiographs revealed a distal one-third shaft tibia and fibula fracture bilaterally managed with closed nailing bilaterally and subsequently mobilized. Both patients had HIV infection since 10 and 14 years, respectively, and were on combination ART.

**Conclusion:** There should be a high index of suspicion to the possibility of fragility fractures in HIV affected patients on ART. Principles of fracture fixation and early mobilization should be followed.

**Keywords:** Human immunodeficiency virus, fragility fractures, anti-retroviral therapy, bilateral fractures.

## Introduction

There are approximately 37.7 million people living with human immunodeficiency virus (HIV) acquired-immune deficiency syndrome (AIDS) in the world of which 28.2 million people receive antiretroviral therapy (ART) [1].

ART has been noted to reduce viral load, improve immunological status, and increase the life expectancy significantly, but it also leads to long term adverse effects such as dyslipidemia, diabetes mellitus, and skeletal fragility [2, 3].

It has been noted that both HIV infection and ART individually

lead to bone metabolic disorders and delay fracture healing; hence, these patients have an increased propensity for fractures following trivial injury and subsequent delayed healing [4, 5].

We present two cases having HIV-AIDS on ART who developed bilateral lower limb fragility fractures following trivial trauma and were managed surgically to highlight the possibility of association between patients with HIV on ART and such fractures. In addition, literature regarding similar cases and their management was reviewed.

## Case Report

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## Author's Photo Gallery



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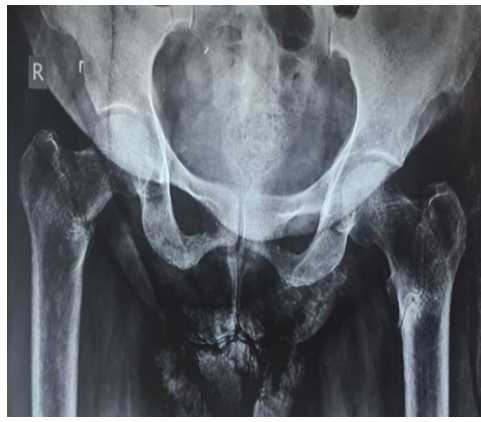
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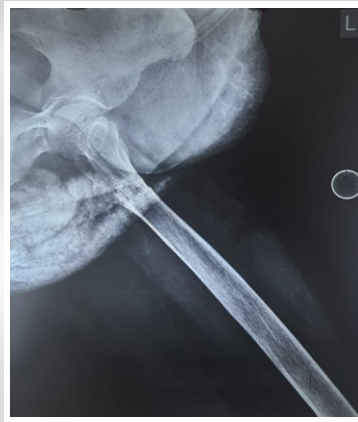
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**Figure 1:** Pre-operative anteroposterior view of pelvis with both hips.



**Figure 2:** Pre-operative left hip lateral view.



**Figure 3:** Pre-operative right hip lateral view.

### Case 1

A 52-year-old female presented to us with pain in the right hip and inability to bear weight since 1 week ago following an episode of trivial fall, the patient also gave a history of dull aching pain in the left hip since the past 2 months. Bilateral hip examination revealed tenderness in both the proximal thigh, with flexion and external rotation deformity of the right lower limb. On subsequent X-rays, it was found that the patient had a right sided intertrochanteric fracture and a left-sided undisplaced unicortical fracture at the level of the lesser trochanter.

The patient was a diagnosed case of HIV on ART comprising dolutegravir, lamivudine, and tenofovir since past 10 years.

The patient was operated with closed reduction and internal fixation with a proximal femoral nail bilaterally. Post-operative period was uneventful and the patient was wheelchair mobilized initially and discharged after 5 days. The patient gradually progressed later to walking with the aid of a walker.

A subsequent follow-up at 3 months revealed a uniting fracture bilaterally.

### Case 2

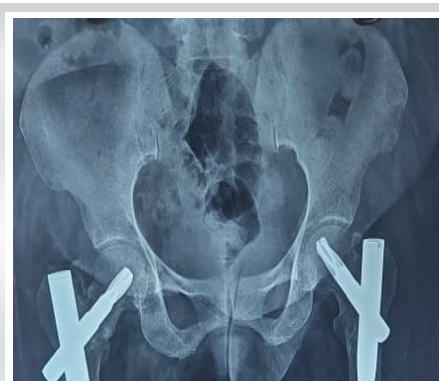
A 70-year-old female presented with pain and swelling in both legs since 3 days following trivial trauma, with tenderness in both the legs. The X-rays revealed a fracture of the distal one-third shaft of tibia, bilaterally, with fracture of the bilateral fibula shaft at the same level.

The patient was a diagnosed case of HIV on ART comprising dolutegravir, lamivudine, and tenofovir since past 14 years.

The patient was managed surgically with closed reduction internal fixation with Intra-medullary interlocking nailing. Post-operative period was uneventful and the patient was wheelchair mobilized initially and discharged after 5 days. The patient gradually progressed later to walking with the aid of a walker.

A subsequent follow-up at 3 months revealed a uniting fracture bilaterally.

Appropriate calcium, vitamin D supplementation, and bisphosphonates were given to both the patients in the pre- and post-operative period to correct metabolic derangements and



**Figure 4:** Post-operative anteroposterior view.



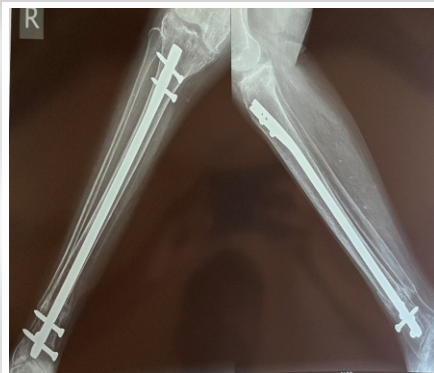
**Figure 5:** Post-operative left hip lateral view.



**Figure 6:** Post-operative right hip lateral view.



**Figure 7:** Pre-operative right tibia.



**Figure 8:** Post-operative right tibia.

taking ART, BMD was found to decrease after initiation of ART and stabilize later on [17]. There is 6% decrease in the BMD in the first 2 years post initiation of ART, irrespective of the drugs used. The mechanism is thought to be multifactorial, but, in part, is due to a direct effect on the osteoblasts and osteoclasts and increased catabolism of vitamin D along with mitochondrial damage [18].

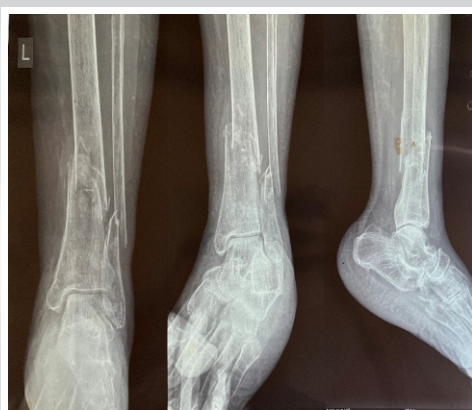
Tenofovir, a nucleoside reverse-transcriptase inhibitors (NRTIs), is known

to aid fracture union.

### Discussion

HIV infection and ART have both been shown to reduce bone mineral density (BMD), mineralization, and bone turnover. A reduced BMD is thought to be associated with a reduced rate of fracture healing; hence, HIV-positive individuals are not only at an increased risk of fragility fractures but also of delayed fracture healing and failure of fracture fixation [6,7,8,9,10].

The prevalence of osteopenia in HIV infected individuals is 15%, that is, 3 times compared to uninfected controls; hence, they have an increased risk of fractures, the osteopenia is thought to be due to chronic inflammation directly leading to increased bony resorption and due to direct action on the osteoclastic activity [4, 11, 12]. There is a disturbance in the synchronized bone remodeling process as suggested by the raised osteocalcin, c-telopeptide, and TNF-alpha levels, which have shown to affect osteoclast function, in HIV-affected individuals. HIV is also known to be associated with osteonecrosis secondary to disruption of osseous blood supply which can in turn lead to delays in bone healing and may also result in non-unions [13, 14, 15]. HIV-infected postmenopausal women have lower BMD, increased bone turnover, and higher rates of bone loss than non-HIV infected women. This is because estrogen mitigates the proresorptive effects of inflammatory cytokines, which are up-regulated in HIV infection; hence, bone loss may be accelerated in HIV-infected postmenopausal women during the menopausal transition stage placing these women at increased risk for fracture [16]. Brown and Qaqish also noted that the prevalence of osteopenia was significantly higher in those individuals



**Figure 9:** Pre-operative left tibia.



**Figure 10:** Post-operative left tibia.

to cause proximal renal tubulopathy with hypophosphatemia, hypokalemia, and metabolic acidosis affecting bone mineralization, leading to osteomalacia with multiple bone pains, weakness and fractures. The condition is managed by cessation of use of tenofovir and by electrolyte correction. In those presenting with renal fanconi syndrome, tenofovir may be substituted with other ART drugs [19].

Zidovudine an NRTI is also known to cause increased osteoclastic activity and hence bone loss.

NRTI and protease inhibitors cause decrease BMD, with protease inhibitors having risk of vitamin D deficiency as well. Dolutegravir containing regimens are thought to be excellent options to reduce the impact of ART on bone, especially in patients with low BMD, to reduce bone loss and fracture risk [20].

Overall, it is necessary to be aware of the association between fragility fractures and ART, to allow for the early diagnosis and management of such patients.

### Conclusion

There should be a strong index of suspicion to the possibility of fragility fractures in patients with HIV on ART, having complaints of bony pains.

| S. No. | Blood Parameter                                  | Pre-op               | Post-op 1 month     |
|--------|--|----------------------|---------------------|
| 1      | Hemoglobin                                       | 9.2 g/dL             | 10.4 g/dL           |
| 2      | Calcium  | 8.9 mg/dL            | 9.2 mg/dL           |
| 3      | Phosphorus                                       | 2.7 mg/dL            | 3.4 mg/dL           |
| 4      | ALP  | 350 U/L              | 120 U/L             |
| 5      | Vitamin D3                                       | 25.3 mg/mL           | 42.1 mg/mL          |
| 6      | iPTH   | 153.6 pg/mL          | 35.4 pg/mL          |
| 7      | Na <sup>+</sup> /K <sup>+</sup> /Cl <sup>-</sup> | 130/2.9/102 mEq/L    | 131/3.0/104 mEq/L   |
| 8      | Viral load                                       | 40 copies HIV RNA/mL |                     |
| 9      | CD4+count  | 450/mm <sup>3</sup>  | 450/mm <sup>3</sup> |

**Table 1:** A detailed blood work-up showed a well-controlled HIV-infection with following blood parameters

Surgical principles of fracture fixation remain similar as in other patients; however, a thorough metabolic work-up should be undertaken and other contributory factors should be investigated and treated accordingly.

To reduce the chances of osteoporosis and associated fragility fractures in patients of HIV on ART, daily vitamin D supplementation has been recommended, and other measures such as calcium supplementation, bisphosphonates, and weight-bearing exercises have also been recommended.

A collaborative approach between orthopedic surgeons and

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Conflict of interest:** Nil **Source of support:** None

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| S. No. | Blood parameter                                  | Pre-op              | Post-op 1 month     |
|--------|--|---------------------|---------------------|
| 1      | Hemoglobin                                       | 8.4 g/dL            | 9.2 g/dL            |
| 2      | Calcium  | 8 mg/dL             | 9.37 mg/dL          |
| 3      | Phosphorus                                       | 3.9 mg/dL           | 4.2 mg/dL           |
| 4      | ALP  | 830 U/L             | 180 U/L             |
| 5      | Vitamin D3                                       | 6.86 mg/mL          | 36.78 mg/mL         |
| 6      | iPTH   | 133.10 pg/mL        | 21.60 pg/mL         |
| 7      | Na <sup>+</sup> /K <sup>+</sup> /Cl <sup>-</sup> | 128/3.1/100 mEq/L   | 132/3.3/102 mEq/L   |
| 8      | Viral Load                                       | 40 HIV RNA/mL       |                     |
| 9      | CD4+ Count                                       | 400/mm <sup>3</sup> | 400/mm <sup>3</sup> |

**Table 2:** A detailed blood work-up showed a well-controlled HIV-infection with the following blood parameters

other specialties is required to bring about optimal results in such patients.

## Clinical Message

A high index of suspicion should be there to the possibility of fragility fractures in patients of HIV on ART. They should be managed following principles of fracture management, along with correction of the metabolic abnormalities.

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