CASE SERIES

Characteristics of foot fractures in HIV-infected patients previously treated with tenofovir versus non-tenofovir-containing highly active antiretroviral therapy

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Summary: In a retrospective case series study, medical records were evaluated for all male patients infected with human immunodeficiency virus (HIV) diagnosed over a one-year period with foot fractures (n = 30) confirmed by magnetic resonance imaging at a Los Angeles outpatient private practice rheumatology clinic. Proportionally more patients had received tenofovir prefracture (17 [57%]) than those who had not (13 [43%]). At fracture diagnosis, these two groups were similar in median age (49 versus 48 years), HIV-1 RNA (both 1.7 $\log_{10}$ copies/mL), CD4 count (300 versus 364/mm^3), time between HIV diagnosis and foot fracture (both 17 years), family history of degenerative bone disease (24% versus 23%), prevalence of malabsorption syndrome, renal failure, calcium deficiency, or vitamin D deficiency, and concurrent use of bisphosphonates, calcitonin, and diuretics. However, more tenofovir-treated patients had osteoporosis (35% versus 8%), stress-type fractures (53% versus 31%), concurrent fractures (12% versus 0%), wasting syndrome (29% versus 15%), truncal obesity (18% versus 8%), smoked cigarettes (more than one pack/day for more than one year; 35% versus 8%), dual energy X-ray absorptiometry (DEXA) T scores < −2.4 (denoting osteoporosis) at the femur (24% versus 9%) and spine (47% versus 36%), and had received protease inhibitors (71% versus 46%), non-nucleoside reverse transcriptase inhibitors (24% versus 0%), prednisone (24% versus 0%), testosterone (47% versus 23%), and teriparatide (29% versus 8%). Median time from tenofovir initiation until fracture was 2.57 (range 1.17–5.69) years. In conclusion, more foot fractures were observed in tenofovir-treated patients than in non-tenofovir-treated patients with HIV infection. Comorbidities and/or coadministered drugs may have been contributory.

Keywords: HIV infection, fractures, antiretroviral therapy, tenofovir

Introduction

Fractures among patients infected with human immunodeficiency virus (HIV) have been the focus of an increasing number of studies since 2000.[1–17] Such fractures have been documented to occur more frequently than in people not infected by HIV[6] and to involve longer healing times and an increased risk of infection.[18] The large US prospective cohort HIV Outpatient Study (n = 5826) reported that, in 2006, the frequency of all fractures among HIV-infected patients aged 25–54 years was over two-fold higher than in the US general outpatient population (84.2 versus 35.6 fractures per 10,000 people, adjusted for gender).[6] HIV-infected patients have been shown to be at particularly high risk for developing fractures if they are aged ≥47 years (compared with ≤35 years), have a history of CD4 cell count below 200/mm^3, have diabetes or

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hepatitis C coinfection, or are an intravenous drug user.[6] Because combination antiretroviral therapy has allowed more and more HIV-infected people to live well beyond 50 years, when osteoblastic activity significantly declines,[1] the occurrence of fractures is expected to increase in this population in the future.

The higher prevalence of fractures among HIV-infected patients compared with the general population is due in part to their lower bone mineral density, which makes their bones more fragile and susceptible to breaking.[1,4,6,13] This is reflected in their six-fold higher rate of osteopenia and nearly four-fold higher rate of osteoporosis.[6] For every one standard deviation reduction in vertebral bone mineral density, there is a two-fold increased risk of vertebral fracture.[1] HIV itself appears to lower bone mineral density due to the presence of increased levels of certain proinflammatory cytokines (interleukin-1, interleukin-6, and tumor necrosis factor) that directly accelerate bone loss.[13]

Many antiretroviral and nonantiretroviral drugs are also known to contribute to low bone mineral density through a variety of mechanisms, including enhanced osteoclastic activity, reduction in osteoblastic activity, impaired calcium absorption, and renal phosphate wasting.[8,13] Of the reverse transcriptase inhibitors, the nucleotide, tenofovir disoproxil fumarate, has been most documented to produce significant reductions in bone mineral density following initiation of therapy.[10,19–25] In clinical trials that have directly compared tenofovir with the nucleoside reverse transcriptase inhibitors, ie, stavudine, zidovudine, and abacavir, tenofovir was found to reduce bone mineral density to a greater degree.[22,26,27] In a cross-sectional observational study by Guillemi et al[10] in 285 unselected adult HIV patients (80% Caucasian, 85% male, median age 48 years), multivariate analysis revealed that tenofovir exposure for at least three months and lower body mass index, but not exposure to other nucleosides or protease inhibitors, were risk factors for low bone mineral density.

To date, studies of fractures in HIV-infected patients have focused primarily on fractures of the hip and spine, as confirmed by dual energy X-ray absorptiometry (DEXA) or magnetic resonance imaging.[4,14,18,21,28] Fractures of the feet have rarely been mentioned in any publication. Considering their weight-bearing role, feet would be expected to be highly vulnerable to fracture in HIV patients, especially those with reduced bone mineral density and the common HIV-associated peripheral neuropathy. The purpose of the present study was to describe the clinical, laboratory, and medical history characteristics of all male HIV-infected patients diagnosed with foot fractures within a one-year period at a private practice rheumatology clinic in Los Angeles, and to differentiate these characteristics in tenofovir-treated versus non-tenofovir-treated patients.

Materials and methods

In this retrospective case series study (COL109415), a rheumatologist (AAH) and podiatrist (RJJ) reviewed the medical records for all male HIV-infected patients in Los Angeles area outpatient podiatry and rheumatology clinics who had been diagnosed as having foot fractures confirmed by magnetic resonance imaging (n = 30) over a one-year period (2006–2007). In most cases, the patients had been seen initially in private podiatry clinics in Los Angeles and were referred to the Center for Rheumatology. However, some patients were seen first at the Center for Rheumatology and were then referred to RJJ's private podiatry practice for foot fracture assessment. Female fracture patients were excluded from the study because it was felt that their greater fracture risk due to lower bone mineral density and bone mass,[29] and the complication of premenopausal and postmenopausal estrogen use (oral contraceptives and estrogen supplements,[30] respectively) could lead to data that would not be comparable with that from a solely male population. Fracture data were included for analysis only for patients whose fractures had occurred either in the absence of trauma or after only trivial trauma. Medical records for patients with fractures due to high-energy traumatic injury (eg, a motor vehicle accident) were excluded from analysis. Excel® sheets were used to capture data pertaining to the patients' demographics, HIV history, comorbidities, alcohol intake, smoking history, highly active antiretroviral therapy (HAART)/non-HIV drug prescription history, bone mineral density scores by DEXA, fracture type, and laboratory values (especially serum calcium, phosphorus, alkaline phosphatase, thyroid-stimulating hormone, 25-hydroxyvitamin D, and parathyroid hormone).

The investigators also noted the characteristics of the foot fracture events, which included the situation surrounding the fracture, location/type of fracture, the presence of concurrent fractures in other body regions, the time between HIV diagnosis and foot fracture occurrence, the time between the start of a particular treatment and foot fracture, and how fractures were managed. Statistical analysis was primarily descriptive, although stepwise logistic regression analyses were performed to evaluate a correlation between the category variables, ie, femur DEXA T scores <-1.5 or ≥-1.5

or spine DEXA T scores <-1.5 or ≥-1.5, and independent variables (baseline demographic characteristics, HIV-1 RNA, CD4 cell count, laboratory values, comorbidities, and concurrently administered drugs).

Results

Foot fractures primarily affected the metatarsal areas. These fractures were marked by pain, often of the pinpoint type when the fracture area was touched, with concomitant swelling and little or no bruising. Proportionally more patients with foot fractures had received tenofovir-containing antiretroviral (17 [57%]) than non-tenofovir-containing antiretroviral (13 [43%]) drugs prior to the fracture. Median time from tenofovir initiation until fracture was 2.57 (range 1.17–5.69) years. At the time fracture was diagnosed, the tenofovir and non-tenofovir groups did not differ significantly in median or mean age (49 versus 48 years and 50.0 versus 54.2 years, respectively). Although there were outliers in age in each of these groups, ie, a 63-year-old in the tenofovir group and an 80-year-old in the non-tenofovir group, most of the patients were in their mid to late forties. The tenofovir and non-tenofovir groups were also similar with respect to baseline viral load (2.1 versus 2.4 $\log_{10}$ copies/mL), time between HIV diagnosis and foot fracture (both 17.0 years), proportion of fractures affecting the metatarsophalangeal area (12% versus 15%), incidence of concurrent vertebral fracture (12% versus 15% of all foot fracture cases), and family history of osteoporosis (24% versus 23% of cases, Table 1). No between-group differences were observed regarding presence of most comorbidities, including hypogonadism, hypertension, malabsorption syndrome, renal failure, calcium deficiency, or vitamin D deficiency, nor were differences seen in serum laboratory values for calcium, albumin, potassium, blood urea nitrogen, sodium, creatinine, chloride, glucose, liver enzymes, and hematocrit.

More patients in the tenofovir group than in the nontenofovir group were osteoporotic, smoked cigarettes regularly, and had truncal obesity and wasting syndrome. Fewer tenofovir-treated patients had a history of alcoholism and anemia secondary to chronic disease. The tenofovir group had higher median plasma concentrations of alkaline phosphatase (104 IU/L versus 72 IU/L), parathyroid hormone (41 pg/mL versus 32 pg/mL), 25-hydroxyvitamin D (37 ng/mL versus 26 ng/mL), and a lower median white blood cell count ($5.5 \times 10^3/mm^3$ versus $6.3 \times 10^3/mm^3$). Evaluation of prior nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, and protease

Table 1 Characteristics of the study patients in each arm

Variable	TDF-containing HAART (n = 17)	Non-TDF-containing HAART (n = 13)
Age, years; median (range)	49 (40–63)	48 (44–80)
Caucasian: Black ratio	13 (76%):2 (18%)	12 (100%):0
Weight, kg; median (range)	80 (61–116)	72 (57–103)
HIV-1 RNA, $\log_{10}$ copies/mL;		
Median (range)	1.7 (1.7–4.7)	1.7 (1.7–4.6)
$<$50, n (%)	14 (82%)	8 (73%)
$\geq$50, n (%)	3 (18%)	3 (27%)
CD4 cell count, cells/mm³;		
Median (range)	300 (150–700)	364 (100–650)
$<$200, n (%)	1 (6%)	3 (27%)
$\geq$200, n (%)	16 (94%)	8 (73%)
Type of fracture		
Stress fracture	9 (53%)	4 (31%)
Laboratory values (mean)		
Alkaline phosphatase (IU/L)	103.5	72.0
Calcium (mg/dL)	9.5	9.4
WBC (thousand cells/mm³)	5.5	6.3
Parathyroid hormone (pg/mL)	40.8	32.0
25-Hydroxyvitamin D (ng/mL)	36.8	26.0
Comorbidities		
Osteoporosis	7 (41%)	3 (23%)
Smoker (chronic, $>$1 pack/day)	6 (35%)	1 (8%)
Wasting syndrome	5 (29%)	2 (15%)
Alcoholism	2 (12%)	4 (31%)
Concurrent fractures	2 (12%)	0
Anemia due to chronic disease	0	3 (23%)
Truncal obesity	3 (18%)	1 (8%)
Concurrent drugs		
Protease inhibitor*	12 (71%)	6 (46%)
NNRTI†	6 (35%)	2 (15%)
Prednisone	4 (24%)	0
Calcium supplements	17 (100%)	11 (85%)
Vitamin D supplements	17 (100%)	11 (85%)
Testosterone	8 (47%)	3 (23%)
Teriparatide	5 (29%)	1 (8%)
DEXA scan category*‡		
Femur T score		
−2.4 to −1.5 (osteopenia)	7 (41%)	4 (36%)
−2.4 (osteoporosis)	4 (24%)	1 (9%)
Spine T score		
−2.4 to −1.5 (osteopenia)	6 (35%)	4 (36%)
$<$−2.4 (osteoporosis)	8 (47%)	4 (36%)

Notes: *In the TDF and non-TDF groups, protease inhibitors were lopinavir/ritonavir (9 versus 3), ritonavir (4 versus 1), atazanavir (3 versus 0), fosamprenavir (1 versus 1), darunavir (0 versus 1), and indinavir (0 versus 1); †NNRTIs were nevirapine (3 versus 2) and efavirenz (3 versus 0); ‡Logistic regression analysis showed a relationship between femur DEXA T scores $<$−1.5 and body weight ($P = 0.036$) and serum glucose ($P = 0.034$). No relationship was seen between femur or spine DEXA T scores $<$−1.5 or $<$−2.4 and alendronate or testosterone use, serum creatinine, blood urea nitrogen, electrolytes, or 25-hydroxyvitamin D.
Abbreviations: TDF, tenofovir; DEXA, dual energy X-ray absorptiometry; NNRTI, non-nucleoside reverse transcriptase inhibitors; WBC, white blood cells; HAART, highly active antiretroviral therapy.

inhibitor use showed that more patients in the tenofovir group had taken lopinavir/ritonavir (53% versus 23%) and ritonavir (24% versus 8%), whereas more patients in the non-tenofovir group had taken abacavir/lamivudine (31% versus 6%). No between-group differences were observed in the frequency of use of any other individual antiretroviral agents.

Logistic regression analyses showed a significant relationship between femur DEXA T-scores <−1.5 and decreased body weight ($P = 0.036$) and increased serum glucose ($P = 0.03$). No relationship was seen between femur or spine DEXA T scores <−1.5 and alendronate use or testosterone use, serum creatinine, serum blood urea nitrogen, electrolytes, or 25-hydroxyvitamin D levels.

The fractures were treated with immobilization of the foot, often with the aid of a casted stiff-soled shoe to be worn to prevent pressure or bending of the fracture area. Surgery was not required, and crutches were generally needed only for metatarsal base injuries. With these precautions, fractures usually required 4–6 weeks to heal fully. In tenofovir-treated patients, tenofovir was generally retained in regimens. Following healing, custom orthotics were created for the patients for insertion into shoes to reduce pressure on the previously fractured foot areas. For patients whose bone mineral density values demonstrated osteoporosis or osteopenia, treatment with supplemental calcium, vitamin D, bisphosphonates, or teriparatide was considered.

Discussion

This small pilot study suggests that foot fractures may occur more often in HIV-infected patients treated with tenofovir-containing HAART than non-tenofovir-containing HAART. Concern about an association of tenofovir with fractures was initially raised by preclinical studies that showed a higher risk of spontaneous fractures and bone abnormalities in rhesus monkeys with simian immunodeficiency virus infection administered supratherapeutic doses of tenofovir (30 mg/kg/day) subcutaneously for one week to 24 months (mean, 14 months) compared with no treatment.[31] These bone effects were associated with elevated alkaline phosphatase levels and decreased serum phosphorus levels. Histomorphometric assessment of the tibial diaphyses in tenofovir-treated monkeys revealed increased osteoid seam width, consistent with defective mineralization of new bone, despite reduction or reversal of tibial bone resorption. A further preclinical study reported completely unmineralized secondary osteons in the tibia of a 16-month-old rhesus monkey whose mother had received high doses of tenofovir while pregnant.[32]

Clinical trials evaluating tenofovir have also demonstrated the adverse effect of the drug on bone. In GS-99-903, a clinical registration trial that compared tenofovir/lamivudine/efavirenz (n = 299) with stavudine/lamivudine/efavirenz (n = 303) in antiretroviral-naïve patients, tenofovir-treated patients experienced a significantly greater mean percentage decrease from baseline in lumbar spine bone mineral density at week 144 (−2.2% versus −1.0% stavudine, $P = 0.001$) and a trend for greater bone mineral density reduction at the hip (−2.8% versus −2.4% stavudine, $P = 0.06$).[26]

Two subsequent clinical trials similarly showed that tenofovir, whether combined with emtricitabine or lamivudine, caused significantly greater bone mineral density reduction than comparator nucleoside reverse transcriptase inhibitor backbones.[21,28] However, none of these clinical trials reported a significantly higher frequency of fractures in tenofovir-treated patients despite the tenofovir-associated reduction in bone mineral density. This underscores clinical evidence demonstrating that reduced bone mineral density is just one contributor to fractures and that bone mineral density alone cannot serve as the only predictor of fracture. In fact, reduced bone mineral density alone generally imparts less than 25% increased risk of vertebral fractures.[33] The effect of decreased bone mineral density on foot fracture risk has yet to be investigated.

Where fracture data have been reported previously in HIV-infected patients receiving HAART, these have dealt primarily with vertebral fractures rather than foot fractures. In fact, in an assessment of patient medical records of approximately 8600 HIV-infected patients (78% male, 70% Caucasian, median age 45 years, 46% smokers, 81% of the HAART regimens including one protease inhibitor and 22% including tenofovir) at nine US HIV clinics, 55% of 55 fractures observed were vertebral, only one of which occurred with a concurrent foot fracture.[14] The other most frequent sites of fracture were the lower extremities (27%, which could have included foot fractures, although these were not specified), upper extremities (6%), and clavicle (4%). The regimens associated with these fractures were not delineated. As in our study, patients who had fractures generally remained on the antiretroviral treatment they had been receiving at the time fracture occurred, and remediation similarly consisted of immobilization of the fracture areas, with institution of calcium, vitamin D, and bisphosphonates if osteoporosis had been detected by bone mineral density measurements.

Foot fractures believed to be related to tenofovir were previously reported in several HIV-infected patients, aged

37–62 years, 12–17 months after tenofovir was added to their HAART regimens.[24,34,35] Their regimens also included either ritonavir-boosted atazanavir or lopinavir. In these cases, bone scintigraphy revealed concurrent fissure fractures in multiple body areas, especially the legs, ribs, pelvis, and femur. Laboratory work confirmed osteomalacia that was likely due to tenofovir-related proximal renal tubular dysfunction, which was marked by phosphaturia, proteinuria, glycosuria, and calciuria. Tenofovir was discontinued, remedial oral 25-hydroxyvitamin D3, neutral sodium-potassium phosphate, and/or calcitriol treatment was initiated, and the condition of the patients resolved and laboratory values and renal function usually normalized within 12 weeks. Generalized fractures in 12 of 22 patients who had developed proximal renal tubular dysfunction secondary to tenofovir were also reported by Woodward et al.[25] In these patients, phosphaturia led to hypophosphatemia, which in turn led to osteomalacia and fracture. In the tenofovir-treated patients in our study, osteomalacia could not be ruled out as a potential cause of, or prodromal condition for, foot fractures because we did not have serum phosphate data, or urinary phosphate, glucose, or protein data. Our tenofovir cohort did not present with a greater number of symptoms suggestive of generalized osteomalacia (diffuse body pain and muscle weakness) than did the non-tenofovir group. However, it did have more stress-type and concurrent fractures and higher parathyroid hormone and alkaline phosphatase levels, all of which are often associated with osteomalacia.[36]

Both the tenofovir and non-tenofovir groups in our study had several factors that could have influenced the occurrence of foot fractures. A larger proportion of tenofovir-treated patients took the protease inhibitor lopinavir/ritonavir concurrently. Because lopinavir/ritonavir increases tenofovir blood levels by inhibiting the efflux of tenofovir out of renal proximal tubule cells and reduces tenofovir renal clearance, the increased tenofovir blood levels during concurrent use could have potentially increased fracture risk, in view of animal studies linking higher tenofovir concentrations with greater demineralization.[31,32] In addition, lopinavir/ritonavir in the absence of coadministered tenofovir has been linked with low bone mineral density and cases of accelerated osteoporosis,[37] and with vertebral fractures.[38] More of our tenofovir-treated cohort took oral corticosteroids, were chronic cigarette smokers, and had truncal obesity or wasting syndrome, all of which have been implicated in reducing bone mineral density.[39–42] These factors could have contributed to the higher frequency of osteoporosis or osteopenia in the tenofovir group, and hence greater likelihood of foot bone

fragility and fracture. These risk factors were likely partially counterbalanced by the greater frequency of use of calcium supplements, vitamin D, testosterone, and teriparatide, ie, drugs that could increase bone mineral density, in the tenofovir group.[43–47] It was not clear in some cases when these were started with respect to the timing of a diagnosis of osteopenia or osteoporosis. Although fewer patients in the non-tenofovir group had as many of these bone mineral density-reducing factors, more non-tenofovir-treated patients were alcoholics or had CD4 counts $<200/mm^3$, both of which can lower bone mineral density.[43,46]

Our study was limited by its small population and its lack of information about the dietary habits and exercise patterns of the patients, both of which could have potentially impacted bone strength, and hence, foot fracture risk. The study involved HIV-infected patients who were diagnosed over a one-year period (2006–2007) after having received tenofovir on average for about 2.5 years. Thus, they were prescribed tenofovir at a time when the nucleoside backbones popularly used in practice were lamivudine/zidovudine, abacavir/lamivudine, and abacavir/lamivudine/zidovudine. It is noteworthy that tenofovir is currently prescribed much more often as a backbone in combination HAART regimens. Thus, if foot fractures were to be evaluated over the past year in HAART-treated patients, the attributability of the fracture to tenofovir use could be debatable because more fractures might only reflect greater prevalence of tenofovir use in current clinical practice. Our study had several attributes, including the fact that the patients were well matched for severity of HIV condition, family history of bone abnormalities, and time between HIV diagnosis and foot fracture diagnosis. Most of the patients were not elderly, and so the effects of older age on bone fragility were negligible. The same data-gathering tool and questions were used in evaluating patient medical charts. Lastly, only males were evaluated because women have a notably higher frequency of low bone mineral density due to smaller body weight and hormonal factors.

In conclusion, this small pilot study suggests a greater incidence of foot fractures in HIV-infected patients on tenofovir-containing than non-tenofovir-containing HAART. Comorbidities and/or coadministered drugs may have influenced the occurrence of these fractures. When choosing antiretroviral agents for inclusion in HAART regimens, it is important for clinicians to consider the potential for drugs to increase the risk of fracture, especially in HIV-infected patients in whom bone mineral density is already diminished.

Disclosure

The results of this study were presented in part in poster 100 at the annual meeting of the American College of Clinical Pharmacy, 19–22 October 2008, Louisville, KY; and in poster 5 at HIV DART 2006 – Frontiers in Drug Development for Antiretroviral Therapies, 9–12 December 2008, Rio Grande, Puerto Rico. This study was funded by a grant from GlaxoSmithKline.

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