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Factors associated with fractures in HIV-infected persons: which factors matter?

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Abstract

Purpose—Growing evidence suggests that tenofovir disoproxil fumarate decreases bone density among patients with HIV, but there are conflicting reports as to whether this decrease in bone density translates to higher fracture risk. We aimed to determine whether tenofovir is associated with elevated fracture risk as compared to other antiretroviral (ART) medications.

Methods—We conducted a retrospective cohort study at two tertiary care hospitals in Boston, MA between 2001 and 2012 to determine whether tenofovir use is associated with elevated all-site fracture risk as compared to other antiretroviral medications.

Results—We identified 1,981 HIV-infected patients who had at some point used tenofovir and 682 patients who had not. The mean age was 43 years, and 72% were male. The hepatitis C co-infection rate was 28%, about 40% had nadir CD4 count <200, and about 40% had a history of an AIDS-defining illness. We did not find an association between risk of fracture and TDF (aRR 0.8, 95% CI 0.6–1.1). However, co-infection with hepatitis C did increase risk of fracture (aRR 1.6, 95% CI 1.1–2.3), as did nadir CD4 count <200 (aRR 3.1, 95% CI 1.9–5.0) and history of AIDS-defining illness (aRR 1.6, 95% CI 1.1–2.2).

Conclusion—There was no association found between fracture and tenofovir use, but there were associations between co-infection with hepatitis C and markers of advanced HIV disease and fracture.

Keywords

HIV; fracture; tenofovir; anti-retroviral therapy

INTRODUCTION

Literature over the past decade suggests that not only do patients with human immunodeficiency virus (HIV) have higher rates of osteoporosis than those without HIV,⁽¹⁾ but that patients with HIV may fracture at higher rates. This problem was first studied in a large hospital-based database where the prevalence of fracture among patients with HIV was more than 50% higher compared to those patients without HIV.⁽²⁾ There have been several subsequent studies confirming this increased risk of fracture in various populations.^(3–6)

The exact reason for this increased risk of fracture among HIV patients is unknown, although it is likely multifactorial. Patients with HIV may have higher rates of known risk factors for osteoporosis, such as smoking or hepatitis C co-infection.^(7–9) Chronic infection with HIV likely contributes to increased systemic inflammation which has been associated

with increased rates of fracture.^(10–12) In addition, the virus may alter bone regulatory mechanisms leading to further decreases in bone density.⁽¹³⁾

There is a concern that certain antiretroviral medications may contribute to the increased rates of osteoporosis and fracture among the HIV population. For example, the class of protease inhibitors (PI) has been linked to osteoporosis both in epidemiologic studies as well as in a randomized controlled trial.^(14–16) Similarly, the medication tenofovir disoproxil fumarate (TDF), a nucleotide analogue reverse transcriptase inhibitor (NRTI), has been associated with increased rates of osteoporosis. Data from randomized controlled trials suggests that a TDF-based regimen is associated with decreased bone mineral density at one year compared to a regimen with abacavir, another NRTI.^(17,18)

However, there is conflicting data as to whether this decrease in bone density seen with TDF is clinically relevant and leads to increased rates of fracture. Prior studies examining this question have suggested decreased risk of fracture,⁽¹⁹⁾ increased risk of fracture,⁽²⁰⁾ or even no association between TDF and fracture.^(3,5,21,22) These varying results may be due to differing methods used to assess medication use. Some of these studies have classified medication use as ‘ever’ vs ‘never’ exposed to TDF, which may not accurately take into account use at time of fracture or duration of use. Others did not take into consideration the use of combination antiretroviral therapy (ART) or did not adjust for possible confounders like CD4 counts or hepatitis C co-infection. In light of these conflicting results and heterogeneous study designs, we conducted a pharmacoepidemiologic cohort study examining the risk of fracture with use of the TDF as compared to the other common ART non-TDF-containing regimens.

METHODS

Study design and population

We performed a medical record-based cohort study to determine the risk of fracture among TDF users as compared to the TDF-sparing regimens. We selected patients through use of an electronic medical record database (the Research Patient Data Registry, RPDR), that contains patient data from Partners Healthcare, a hospital consortium in Boston, Massachusetts. Patient data from November 1, 2001 to August 29, 2011 from two tertiary care hospitals were searched to identify potentially eligible subjects: individuals who had received a diagnosis of HIV (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]: 042.xx, 043.xx, 044.xx) on two separate visits, and were at least 18 years of age at time of the second visit. The index date of inclusion into study was then defined as the date of first prescription for any ART regimen recorded in the electronic medical record. To be included in the study, patients had to meet all three inclusion criteria. This RPDR definition of HIV diagnosis was validated in a prior study and found to have a positive predictive value (PPV) of 100% (95% CI 93–100%).⁽²³⁾ Subjects were followed until the time of fracture or the last encounter within the study period, whichever came first.

Outcome definition

The primary outcome of interest was fracture at any site, defined through the RPDR by either one diagnostic code or one notation of fracture on a patient's problem list during the study period (see Supplementary Data, Table 1 for diagnostic codes used to define fracture). The RPDR definition of fracture was validated in a prior study and found to have a PPV of 90% (95% CI 79–97%).⁽²³⁾

Exposure definition

The exposure of interest was TDF. The TDF-sparing medications are listed in Supplementary Data, Table 1.

As many subjects take more than one ART medication concurrently, we used a hierarchy of ART medications in which those subjects who had TDF as part of their regimen would be labeled “TDF users” regardless of other medications included in the ART regimen. This type of hierarchy has been utilized in several pharmacoepidemiologic studies attempting to compare medications commonly used in combination.^(24,25)

At the time of inclusion into the study, subjects were followed forward to determine exposure status with respect to our primary exposure of interest. According to the hierarchy noted above, subjects taking a particular medication regimen became a part of the exposure cohort of that medication regimen (i.e. “TDF user”). For example, a subject stopping TDF and switching to another ART would be censored from contributing time to the TDF exposure but would then contribute time as a “non-TDF user.” A subject was considered to be a part of an exposure cohort after a lag period of continuous drug availability for 90 days. This lag period was instituted to reflect the fact that bone mineral metabolic changes from medications do not contribute to fractures immediately but typically take several months. Lag periods such as this have been used in trials of drugs that are known to change fracture risk.⁽²⁶⁾

Covariate definitions and Statistical analysis

Covariates included known risk factors for osteoporosis such as body mass index (BMI) and age as well as prior use of certain medications (e.g. corticosteroids), lifestyle risk factors (e.g. tobacco use), and co-morbidities associated with osteoporosis (e.g. hepatitis C). Certain comorbid conditions were assumed to be non-curable and were coded as present from the time of the first diagnosis date: diabetes, Hepatitis C co-infection, stroke, neoplasm, chronic renal disease, obstructive lung diseases (asthma, COPD), HIV-associated dementia, Parkinson's, Alzheimer's, Crohn's, hyperthyroid, hyperparathyroid, osteoporosis, osteonecrosis. A similar strategy was implemented for alcohol abuse and intravenous drug use – if it was mentioned in at least one medical encounter, the person was marked as having a history of such abuse. Smoking status was dichotomized as never smoker vs. current/past smoker.

We also abstracted HIV-specific covariates from RPDR. CD4 data were re-assessed monthly. RPDR definitions of several covariates of particular interest were validated through chart review of 100 charts. The full list of covariates and their definitions is presented in the

Supplementary Data, Table 1 and the PPVs are presented in the Supplementary Data, Table 2.

The statistical analysis was done in several stages. First, we conducted a series of bivariate analyses using pooled logistic regression. Those factors exhibiting associations with $OR > 1.5$ or $OR < 0.6$ or having p -values < 0.1 were advanced to multivariable analysis, using the pooled logistic regression approach. The variable denoting the use of TDF was retained throughout the model building process, regardless of the associated p -value. We also retained the variables denoting intravenous drug use (IVDU) status and smoking, as these factors have been shown to be related to fractures. Covariates included in the final multivariate model were history of falls, HCV, history of fractures, neoplasms, obstructive lung disorder, osteopenia/osteoporosis, nadir CD4 < 200 cells/mm³, use of steroids, race, and smoking status, IVDU indicators, and current use of TDF.

Ethics statement

This study was approved by the Partners Human Research Committee.

RESULTS

We identified 2,663 patients that met all entry criteria, with 1,981 of these patients using TDF at some point during their follow-up. The mean follow-up time was 3 years. The mean age in the cohort was 43 years, and 72% of the cohort were male. Over a quarter of patients were co-infected with hepatitis C (745 patients, or 28%), and nearly half had a history of an AIDS-defining illness (Table 1).

We found 100 total fractures among TDF users during 4,496 person-years of follow-up, and 80 fractures among non-TDF users during 3,773 person-years of follow-up. Our crude incidence rate of fractures per 1,000 person-years among TDF users was 22.2 (95% CI 17.9–26.6), and 21.2 (95% CI 16.6–25.8) among non-TDF users, with crude incidence rate ratio of 1.0 (95% CI 0.8–1.4) comparing TDF users to non-TDF users.

We then examined the bivariate associations of potential risk factors of fracture in our population (Table 2). We did not find an association between start of follow-up time before and after 2005 (crude RR 1.2 [95% CI 0.9–1.6]). Factors associated with risk of fracture in bivariate analysis included HIV-specific risk factors, such as history of AIDS-defining illness (crude RR 2.1, 95% CI 1.5–2.8) and nadir CD4 count < 200 cells/mm³ (crude RR 3.7, 95% CI 2.3–5.8), as well as traditional risk factors such as osteoporosis (crude RR 3.1, 95% CI 1.9–5.1) and history of falls (crude RR 5.9, 95% CI 4.1–8.4). Factors that protected against fracture included age less than 41 years (crude RR 0.5, 95% CI 0.4–0.8) and non-white race (crude RR 0.7, 95% CI 0.5–0.9). The factors significant in bivariate analyses were included in adjusted multivariate analysis.

We did not observe a statistically significant association between TDF use and fracture in multivariate analyses that adjusted for age, race, and covariates that were associated with fracture in bivariate analysis (adjusted RR (aRR) 0.8, 95% CI 0.6–1.1) (Table 2). We found age less than 41 years to be protective against fracture (aRR 0.7, 95% CI 0.5–1.0). We also

found prior fracture (aRR 1.7, 95% CI 1.1–2.6) and history of falls (aRR 4.9, 95% CI 3.3–7.2) to be predictive of fracture. Co-infection with hepatitis C was associated with risk of fracture (aRR 1.6, 95% CI 1.1–2.3), as was nadir CD4 count <200 cells/mm³ (aRR 3.1, 95% CI 1.9–5.0) and history of AIDS-defining illness (aRR 1.6, 95% CI 1.1–2.2).

DISCUSSION

We examined the risk of fracture among patients with HIV using TDF as compared to those patients using non-TDF regimens. Our study did not find evidence of an increased risk of fracture among TDF users, either in crude analyses or in analyses adjusted for both general risk-factors for fracture as well as HIV-specific factors.

As TDF is part of a first-line therapy regimen for most patients with HIV²⁷, determining its association with fracture has been an important question to answer for clinicians prescribing ART. The association of TDF with low bone density, thought likely due to its effect on the renal tubule leading to phosphate wasting²⁸, is well known. However, in the past decade, studies attempting to answer whether TDF actually leads to fracture have had discrepant results. For example, two major studies published in the last five years have opposite conclusions: Bedimo and others used a large veteran database to show an association of fracture with TDF use²⁰, while Mundy and others studying TDF use in a large database of health-insured patients showed a protective effect of TDF on fracture¹⁹. While these studies and others have raised awareness regarding the potential associations between HIV, ART and fracture, prior studies are limited in either not taking into account current use of TDF, or not taking into account other medications in patients' current ART regimens. We addressed these methodologic issues in our study to better clarify the association of TDF with fracture.

The concern for the potential toxicities of TDF has led investigators to examine other, potentially less toxic formulations of the medication. Tenofovir alafenamide (TAF), has recently been found to be an effective alternative to TDF that has both a lower risk of renal toxicity and less reduction in bone density. However, the effect of TAF on fracture risk remains unknown.⁽²⁹⁾

While we did not document an association of TDF with fracture, we did find that certain HIV-specific factors were associated with fracture in our cohort. In particular, we found associations between fracture and hepatitis C co-infection, a history of nadir CD4<200 cells/mm³ and history of AIDS-defining illness, all of which have been previously noted.^(4,5,20,21,30) However, an abstract examining patients in the Veterans Affairs Healthcare system presented at the 2015 International AIDS Society meeting showed that despite these increased risks of fracture among patients with HIV, rates of screening bone density and vitamin D measurements remain low, even in patients who have already experienced an osteoporotic fracture.^(30,31)

Our study should be interpreted in light of limitations shared by many epidemiologic studies. The electronic medical record (EMR) is a valuable tool to assess rare outcomes but is limited to data entered for clinical purposes. Therefore, certain covariates may not have been recorded for each patient, such as family history of fracture, laboratory values such as

phosphate or vitamin D, or gonadal status, and exposures to medications may not be accurately documented. While we focused on tenofovir use because of its associations with low bone density, we did not assess other antiretroviral therapy regimens in our study. We also did not distinguish between different types of fracture, such as osteoporotic or traumatic. In addition, as we only used the EMR for one health system, it is possible that our study may have missed fractures that were treated at other institutions. Another limitation is that subclinical fractures, such as vertebral fractures, may have been missed as screening x-rays were not able to be performed as part of our retrospective cohort study design.

Our study has unique strengths. We applied careful pharmacoepidemiologic methods, such as the use of a medication hierarchy, to address the complicating factors of current medication use and concomitant medication regimens. In addition, we validated not only our outcome and exposures in our EMR system, but also several important covariates that are known risk factors for fracture.

In summary, these data from a large cohort of HIV-infected patients treated in the two tertiary clinics did not provide evidence that TDF use was associated with greater fracture risk. However, certain HIV-specific risk factors, such as HCV co-infection, nadir CD4 and AIDS-defining illness were associated with higher risk of fracture. Our study lends support to the idea that patients with certain HIV-specific risk factors, such as nadir CD4 <200 cells/mm³, should be considered for further bone density testing to prevent the outcome of fracture.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SUMMARY

This study aims to determine whether an important medication used to treat HIV, tenofovir, is associated with fracture, as prior studies are conflicting. Our study found that while co-infection with hepatitis C and markers of HIV severity were associated with fracture, tenofovir was not.

Table 1

Baseline patient characteristics.

Characteristic [†]	Total Cohort	Ever TDF users	Never TDF users
Sample size	2,663	1,981	682
Age (years), Mean (SD)	43.2 (9.8)	43.2 (9.5)	43.3 (10.6)
Age (years)			
40	1055 (40%)	777 (39%)	278 (41%)
>40	1608 (60%)	1204 (61%)	404 (59%)
Sex			
<i>Male</i>	1918 (72%)	1449 (73%)	469 (69%)
<i>Female</i>	745 (28%)	532 (27%)	213 (31%)
Race			
<i>White</i>	1334 (50%)	1021 (52%)	313 (46%)
<i>Other</i>	1329 (50%)	960 (48%)	369 (54%)
BMI, Mean (SD)	26.3 (5.2)	26.3 (5.2)	26.0 (5.2)
BMI			
Missing	1240 (47%)	893 (45%)	347 (51%)
<18.5	44 (2%)	35 (2%)	9 (1%)
18.5 – 24.9	596 (22%)	444 (22%)	152 (22%)
25.0 – 29.9	514 (19%)	398 (20%)	116 (17%)
30.0	269 (10%)	211 (11%)	58 (9%)
Follow-up time (years), Mean (SD)	3.0 (2.5)	3.1 (2.5)	2.8 (2.6)
Study entry year			
<2005	1084 (41%)	758 (38%)	326 (48%)
2005	1579 (59%)	1223 (62%)	356 (52%)
*Prior fracture	236 (9%)	164 (8%)	72 (11%)
*History of any falls	200 (8%)	156 (8%)	44 (6%)
*Chronic renal failure	226 (8%)	154 (8%)	72 (11%)
*Obstructive lung disease	604 (23%)	451 (23%)	153 (22%)
Osteonecrosis	36 (1%)	28 (1%)	8 (1%)
Osteoporosis	107 (4%)	77 (4%)	30 (4%)
Hyperparathyroidism	20 (1%)	15 (1%)	5 (1%)
Steroid use	724 (27%)	563 (28%)	161 (24%)
Calcium supplement use	177 (7%)	138 (7%)	39 (6%)
Vitamin D supplement use	432 (16%)	341 (17%)	91 (13%)
Tobacco use	972 (37%)	761 (38%)	211 (31%)
Alcohol abuse	405 (15%)	319 (16%)	86 (13%)
Intravenous drug/substance abuse	545 (20%)	422 (21%)	123 (18%)
*Hepatitis C co-infection	745 (28%)	548 (28%)	197 (29%)

Characteristic [†]	Total Cohort	Ever TDF users	Never TDF users
*Nadir CD4 count <200 cells/mm ³	1092 (41%)	872 (44%)	220 (32%)
*History of an AIDS-defining illness	1196 (45%)	929 (47%)	267 (39%)

[†]Unless otherwise indicated, all columns denote (N, %)

*Denotes variables that were measured at each month of follow-up. All other variables were measured at time of entry into the study.

Table 2

Relative risk of fracture among HIV-infected patients

Covariate	Bivariate analysis			Multivariate analysis		
	RR	95% CI	p-value	RR	95% CI	p-value
Current TDF use	1.0	0.8 – 1.4	0.75	0.8	0.6 – 1.1	0.16
Age 40 years	0.5	0.4 – 0.8	<0.01	0.7	0.5 – 1.0	0.05
Female sex	0.9	0.7 – 1.3	0.59			
Non-white race	0.7	0.5 – 0.9	0.02	0.7	0.5 – 1.0	0.02
Study entry year 2005 (vs. <2005)	1.2	0.9 – 1.6	0.25			
Prior fracture	3.1	2.2 – 4.4	<0.01	1.7	1.1 – 2.6	0.01
History of falls	5.9	4.1 – 8.4	<0.01	4.9	3.3 – 7.2	<0.01
Obstructive lung disease (asthma or COPD)	2.1	1.5 – 2.8	<0.01	1.4	1.0 – 1.9	0.07
Vitamin D supplement use	2.2	1.5–3.2	<0.01	1.5	1.0 – 2.3	0.06
Steroid use (ever)	2.2	1.6 – 2.9	<0.01	1.5	1.1 – 2.0	0.02
Alcohol abuse	1.5	1.1 – 2.2	0.02	0.8	0.6 – 1.2	0.35
Hepatitis C co-infection	2.2	1.6 – 3.0	<0.01	1.6	1.1 – 2.3	0.01
Nadir CD4 count <200 cells/mm ³	3.7	2.3 – 5.8	<0.01	3.1	1.9 – 5.0	<0.01
History of an AIDS-defining illness	2.1	1.5 – 2.8	<0.01	1.6	1.1 – 2.2	<0.01
Osteonecrosis	3.9	1.8 – 8.5	<0.01	2.2	1.0 – 5.2	0.06
Osteoporosis	3.1	1.9 – 5.1	<0.01	1.6	0.9 – 2.9	0.09