Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents

Roger Bedimo, Naim M. Maalouf, Song Zhang, Henning Drechsler and Pablo Tebas

Background: While tenofovir (TDF) exposure has been associated with decreased Bone density, it remains unclear whether it is associated with increased risk of osteoporotic fractures (OF).

Methods: Patients with any OF (defined as wrist, vertebral or hip fracture) occurring after HIV diagnosis were identified by ICD-9 code in the Veterans Affairs? Clinical Case Registry from 1988 to 2009. OF risk associated with cumulative exposure to TDF and other antiretrovirals (ARV) was examined in univariate analysis (UV) and multivariate models 1 (MV1 – controlling for race, age, tobacco use, diabetes, body mass index, and hepatitis C status) and model 2 (MV2 – controlling for MV1 variables + concomitant ARV exposures).

Results: Among 56 660 patients evaluated, TDF exposure (total: 46 062 PY) was associated with an OF hazard ratio (HR) of 1.080 (95% CI: 1.02–1.15; $p < 0.001$) in UV analysis; 1.06 (0.99–1.12) in MV1 and 1.06 (0.99–1.14) in MV2. Among patients entering the cohort in the HAART era ($n = 32\,439$), TDF exposure was associated with a yearly HR for OF of 1.16 (95% CI: 1.08–1.24; $p < 0.001$) in UV model, 1.13 (1.05–1.21; $p = 0.001$) in MV1 and 1.12 (1.03–1.21; $p = 0.011$) in MV2. Boosted PI exposure was associated with HR of 1.11 (1.05–1.18; $p = 0.001$) in UV model, 1.08 (1.01–1.15; $p = 0.026$) in MV1 and 1.05 (0.97–1.13; $p = 0.237$) in MV2. Among PIs, Lopinavir/ritonavir (LPV/RTV) had an OF HR of 1.09 (CI: 1.00–1.20; $p = 0.051$) in MV2.

Conclusion: Cumulative exposure to TDF and, among PIs, LPV/RTV were independently predictive of increased risk of OF in the HAART era.

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INTRODUCTION

The introduction of Highly Active Antiretroviral Therapy (HAART) has considerably reduced the mortality of Human Immunodeficiency Virus (HIV)-infected patients in developed countries. Consequently, the HIV prevalence in the general population is growing, and the age of the HIV-infected individuals is increasing, to the point that by 2015, the median age of HIV-infected individuals in the United States is expected to exceed 50 years [1]. The improved survival of HIV-infected patients has already been associated with a shift in the underlying cause of death among these patients, with lesser representation of "AIDS-related causes" and greater representation of "non-AIDS-related" deaths [2]. Low bone mass and osteoporotic fractures have also emerged among the chronic problems affecting this aging HIV-positive population.

A number of studies have described accelerated bone loss and higher rates of osteopenia and osteoporosis among HIV-infected individuals than in the general population [3,4]. Rates of osteoporotic fractures have also been shown to be higher among HIV-infected patients than

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age-matched controls [5,6] While HIV infection itself has adverse skeletal effects, HAART may also contribute to accelerated bone loss [4,7–9]. Previous studies have suggested that antiretroviral drugs (ARVs) differ in their impact on bone health: TDF has been found to be associated with a greater decline in BMD than stavudine [10] or abacavir [11]. Prophylactic use of TDF has also been shown to cause a small but significant decline in BMD in HIV-uninfected subjects [12]. Also, earlier studies had suggested that exposure to PIs decreased BMD [4,13], and it has been recently suggested that atazanavir is associated with increased risk of osteoporosis, compared to efavirenz [11]. Finally, antiretroviral initiation has been shown to be associated with a rapid and significant increase in levels of serologic markers of increased bone turnover (which might signify increased bone fragility) [14–16].

Although these findings have raised concern for increased risk for osteoporotic fractures (OF), there has never been an evaluation of the OF risk associated with cumulative exposure to TDF and other ARVs.

Methods

Data source

Our source of data was the Veterans Health Administration (VHA)'s Clinical Case Registry (CCR), spanning a 21-year period, from 1988 to 2009. The CCR database aggregates detailed demographic, diagnostic, therapeutic and healthcare utilization data on all HIV-infected patients from all VHA facilities to the unique patient level. It comprises VA specific codes for healthcare utilization (hospitalizations and clinic visits), National Pharmacy Benefits Management (PBM) codes for drug utilization, as well as CPT and ICD-9 codes for procedures and diagnoses respectively.

Exposure ascertainment

Patient-days of ARV use prior to OF event were calculated for each ARV, and survival analyses done to predict new OF. PBM data were used to identify supply of each ARV. Exposure time was determined for each ARV or class of ARVs by calculating the number of days covered by each prescription. It was defined as time of cumulative exposure to the ARV or class of ARVs from their initial prescription to the first occurrence of one of the following: 1) development of the first OF episode or death; 2) discontinuation of the ARV; 3) last recorded patient encounter; 4) December 31st, 2009 (date of censure of the dataset).

The following demographic variables were extracted: age, race (Black, White or other), and gender. BMI was calculated annually based on height and weight. For patients whose BMI is missing during certain years, we imputed the missing data by assuming a linear trend in BMI with respect to time. Patients with a value of $<20\,Kg/m^2$ were classified as having low BMI. Patients with diabetes mellitus or tobacco use were identified by the presence of at least one of the ICD-9 codes indicated in Table 1 were listed as their discharge or outpatient diagnoses.

Patients were classified as having chronic kidney disease (CKD) if their estimated glomerular filtration rate (eGFR) was <60 by the MDRD method: GFR (mL/min/1.73 m^2) = **175** x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American).

Outcome ascertainment

Our primary outcome was incident vertebral, hip and wrist fractures (selected on the basis of their likelihood of being related to osteoporosis), and referred to herein after as "osteoporotic fractures" (OF) [17]. These fractures were identified using ICD-9 codes outlined in Table 1. For patients with multiple OF events, only the first one was counted.

Table 1. ICD-9-CM Codes Used to Identify Osteoporotic Fracture Events and Risk Factors.

Exposure and Outcome Measures	ICD-9-CM Codes Used
Hepatitis C Infection	070.41 [acute hepatitis C with hepatic coma], 070.44 [chronic hepatitis C with hepatic coma], 070.51 [acute hepatitis C without mention of hepatic coma], 070.54 [chronic hepatitis C without mention of hepatic coma], V02.62 [hepatitis C carrier].
Diabetes Mellitus	250.0 (diabetes mellitus without mention of complication), 250.1 through 250.9: (diabetes mellitus with complications),
Smoking	305.1 (tobacco use disorder), or V15.82 (history of tobacco use)
Vertebral Fracture	805.2 [closed fracture of dorsal (thoracic) vertebra], 805.3 [open fracture of dorsal (thoracic) vertebra], 805.4 (closed fracture of lumbar vertebra), 805.5 (open fracture of lumbar vertebra), 805.6 (closed fracture of sacrum and coccyx), and 805.7 (open fracture of sacrum and coccyx)
Hip Fracture	820.0 (transcervical fracture, closed), 820.1 (transcervical fracture, open), 820.2 (pertrochanteric fracture of femur, closed), 820.3 (pertrochanteric fracture of femur, open), 820.8 (fracture of unspecified part of neck of femur, closed), and 820.9 (fracture of unspecified part of neck of femur, open)
Wrist Fracture	814.0 (closed fractures of carpal bones), 814.1 (open fractures of carpal bones), 813.4 (fracture of lower end of radius and ulna, closed), and 813.5 (fracture of lower end of radius and ulna, open).

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A validation of ICD-9 codes for ascertainment of fractures in the VA databases (compared to a review of the radiology reports) was done in a recently presented study [18]. It showed a positive predictive value and a negative predictive value of 0.64 and 1.00 respectively, with a level of agreement of 0.97.

Statistical analysis

We summarized the CCR data by mean, median, standard deviation and proportion. Annual and age-group-specific incidence rates were computed for OF. Univariate Cox survival models were used to assess the marginal association between OF and various risk factors, such as age at cohort entry, race, smoking, BMI, CKD, HCV and cumulative ARV exposure. The annual BMI and CKD measurements were included into the model as time-dependent covariates. Categories explored were cumulative exposure to: tenofovir (TDF), abacavir (ABC), AZT or D4T (AZT/D4T) any boosted protease inhibitors (rPI), and non-nucleoside reverse transcriptase inhibitors (NNRTI). Two multivariable models were constructed to examine the association of these ARV exposures with OF: model 1, controlling for age, race, tobacco use, diabetes, CKD, HCV and BMI; and model 2, controlling model 1 variables and concomitant exposure to other ARVs. Gender was not included in the model since over 98% of the study population is male. Statistical significance was declared at $p<0.05$.

Two separate analyses were conducted using these survival models: for the entire study population, and only for patients entering the cohort in the HAART era (since January 1st, 1996).

In the HAART era, we also examined the OF risk associated with specific protease inhibitors with over 10 000 PY of exposure in the database: Nelfinavir (NFV), Indinavir (IDV), Atazanavir (ATV) and Lopinavir/ritonavir (LPV/RTV) in univariate and multivariate models 1 and 2 as above.

All statistical analyses were performed using SAS 9.2 (SAS Institute, Gary, NC).

RESULTS

Study population and treatment exposure

We identified 56 660 patients who used VHA services for HIV disease during the study period and were included in CCR, including 22 005 who had clinic/outpatient or inpatient discharge data within the last twelve months of observation (1 January 2009–31 December 2009). They contributed a total of 305 237 person-years (PY) of follow-up. Among them, 39 277 (69.4%) had at least at least one month of ART exposure, and total ART exposure in the cohort was 164 414 PY. The proportion of male patients was 98%.

Patients with OF had a higher median age than those without (46 years vs. 44), were more likely to be white (57% vs. 45% of those without OF), smokers (56% vs. 32%), to have diabetes (25% vs. 15%), a BMI below 20 (49% vs. 33%) and have HCV co-infection (51% vs. 31%) ($p < 0.0001$ for all comparisons).

Rates of osteoporotic fractures

A total of 951 individual patients sustained at least one OF during the period of observation (124 vertebral, 486 wrist and 341 hip). Rates for both hip and vertebral fractures (per 1000 PY) increased progressively from the 18–29 years age group (0.02 and 0.00 respectively) to the 70+ years age group (4.49 and 1.65 respectively). The rates of wrist fractures increased progressively from the 18–29 years age group (0.11 per 1000 patient-years) to the 50–59 years age group (2.41), then declined in the later age-groups (1.64 for the 60–69 years and 1.20 for the 70+ years).

Cumulative ARV use and risk of osteoporotic fractures: 1988–2009

Unadjusted and adjusted hazard ratio (HR) for OF associated with cumulative exposure to any antiretroviral therapy and traditional osteoporotic risk factors are presented in Table 2.

Figure 1 presents HR for OF associated with different individual ARVs and ARV classes, in univariate and multivariate models described above.

Table 2. Factors predicting osteoporotic fracture among HIV patients.

Factors	Hazard Ratio (95% Confidence Interval; p value) Univariate Analysis	Multi-variable Analysis
Cumulative ART Use (per year)	1.05 (1.01–1.10; p = 0.02)	0.99 (0.95–1.04; p = 0.77)
CKD (eGFR <60)	1.48 (1.04–2.09; p = 0.03)	1.05 (0.72–1.53; p = 0.79)
White Race	1.76 (1.46–2.13; p < 0.0001)	1.88 (1.54–2.30; p < 0.0001)
Age (per 10 year increase)	1.51 (1.39–1.63; p < 0.0001)	1.50 (1.37–1.64; p < 0.0001)
Tobacco Use	1.25 (1.06–1.47; p = 0.01)	1.31 (1.09–1.56; p = 0.003)
Diabetes	1.27 (1.05–1.53; p = 0.01)	1.10 (0.90–1.34; p = 0.34)
BMI < 20	1.61 (1.29–2.00; p < 0.0001)	1.48 (1.18–1.87; p = 0.007)
HCV Co-infection	1.43 (1.21–1.69; p < 0.0001)	1.49 (1.25–1.77; p < 0.0001)

BMI, Body Mass Index; CKD, Chronic Kidney Disease; defined as estimated glomerular filtration rate (eGFR) < 60.

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TDF exposure (46 062 PY) was associated with a yearly HR for OF of 1.08 (95% CI: 1.02–1.15; $p < 0.001$) in UV model, 1.06 (0.99–1.12; $p = 0.079$) in MV1 and 1.06 (0.99–1.14; $p = 0.106$) in MV2. Boosted PI exposure (41 336 PY) was associated with HR of 1.06 (1.01–1.12; $p = 0.015$) in UV model, 1.04 (0.99–1.10; $p = 0.142$) in MV1 and 1.03 (0.97–1.09; $p = 0.349$) in MV2. Exposure to ABC (24 251 PY), AZT/D4T (94 595 PY) or NNRTI (59 857 PY) were not significantly associated with increased risk of OF in UV or MV models.

Cumulative ARV use and risk of osteoporotic fractures in the HAART era: 1996–2009

There were 32 439 patients who entered the cohort in the HAART era (191 258 person-years). As expected, the proportion of patients exposed to antiretroviral therapy was significantly higher among patients who entered the cohort in the HAART era (83.6%, compared to 69.4% in the entire cohort). The rate of osteoporotic fractures was significantly higher in the HAART era (4.09 events/1000 patient-years) compared to the pre-HAART era (1.61 events/1000 patient-years).

For patients who entered the cohort in the HAART era, TDF exposure (38 009 PY) was associated with a yearly HR for OF of 1.16 (95% CI: 1.08–1.24; $p < 0.001$) in UV model, 1.13 (1.05–1.21; $p = 0.001$) in MV1 and 1.12 (1.03–1.21; $p = 0.011$) in MV2. Boosted PI exposure (32 109 PY) was associated with HR of 1.11 (1.05–1.18; $p = 0.001$) in UV model, 1.08 (1.01–1.15; $p = 0.026$) in MV1 and 1.05 (0.97–1.13; $p = 0.237$) in MV2. Exposure to ABC (18 885), AZT/D4T (68 376 PY) or NNRTI (48 943 PY) were again not significantly associated with increased risk of OF in UV or MV models (Fig. 2).

Since exposure to TDF and rPI were the only ones significantly associated with increased OF risk in univariate analysis, we then evaluated the effect of cumulative exposure to both TDF and rPI, and that of exposure to individual rPIs. For this analysis, we determined four different exposure categories: 1) exposure to neither TDF nor rPI (referent category); 2) exposure to TDF, but not rPI; 3) exposure to rPI, but not TDF; and 4) concomitant exposure to TDF and rPI. Concomitant exposure to both TDF and rPI associated with a greater OF risk (HR: 1.16; CI: 1.04–1.30) than exposure to either TDF without rPI (HR: 1.11; CI: 1.01–1.21) or rPI without TDF (HR: 1.10; CI: 1.01–1.22).

Regarding exposure to individual PIs, we selected those with the highest PY of exposure in the database: Indinavir (IDV; 12 124 PY), Atazanavir (ATV; 12 685 PY), Nelfinavir (NFV; 14 356 PY) and Lopinavir/ritonavir (LPV/RTV; 15 319 PY). Only LPV/RTV was associated with significantly increased OF risk in UV model (HR: 1.17; CI: 1.08–1.26; $p < 0.0001$). The association remained significant in MV1 (HR: 1.13; CI: 1.04–1.22; $p = 0.005$) and barely in MV2 (HR: 1.09; CI: 1.00–1.20; $p = 0.051$). Exposure to other PIs (boosted or unboosted) was not associated with significantly increased OF risk (Fig. 3). Also, cumulative exposure to RTV (regardless of dosing used for boosting) was not predictive of fracture risk (HR: 1.06; CI: 0.97–1.15; $p = 0.200$) (Fig. 3). Also, as the dose of RTV used for boosting of other PIs varies, we examined whether RTV dose was associated with OF risk, and it was not (HR: 1.009; $p = 0.279$).

Discussion

The goal of this study was to evaluate the association of antiretroviral exposure and other risk factors with incident OF among HIV-infected patients. Using a cohort of 56 660 HIV-infected patients followed for a mean of 5.4 patient-years, we found for the first time that exposure to TDF and rPI were associated with a modestly increased OF risk. After controlling for traditional OF risk factors, these associations were no longer statistically significant. However, stronger associations between either TDF or rPI with OF were found when analysis was limited to patients who entered the cohort in the HAART era. TDF remained independently predictive of OF risk (12% higher risk per year of exposure) after controlling for traditional OF risk factors and concomitant ARV used.

Furthermore, we found evidence of an interaction between TDF and rPI in their association with OF risk. Concomitant exposure to both TDF and rPI associated with a greater OF risk than exposure to either TDF without rPI, or rPI without TDF.

Among individual PIs, only LPV/RTV was found to be associated with a significantly increased risk of OF. While these could be explained by concomitant use of RTV with LPV, neither RTV alone nor boosted ATV or IDV were associated with increased risk.

The pathogenesis of HIV-associated increased risk of osteoporosis is likely multi-factorial and is incompletely understood. Individuals with HIV infection have a high prevalence of traditional risk factors for osteoporosis – including low body mass index, poor nutrition, frequent glucocorticoid use, smoking, and vitamin D deficiency – as well as co-infection with HCV [6,19]. HIV infection itself may independently be associated with an increased risk of osteoporosis, as it has been shown in studies evaluating BMD in patients naïve to antiretroviral therapy [8,20,21]. This might be mediated through the presence of chronic inflammation and its effects on bone remodeling, and imbalances in the gonadal and calciotropic hormonal systems that regulate bone formation and resorption. ART, particularly immediately after the

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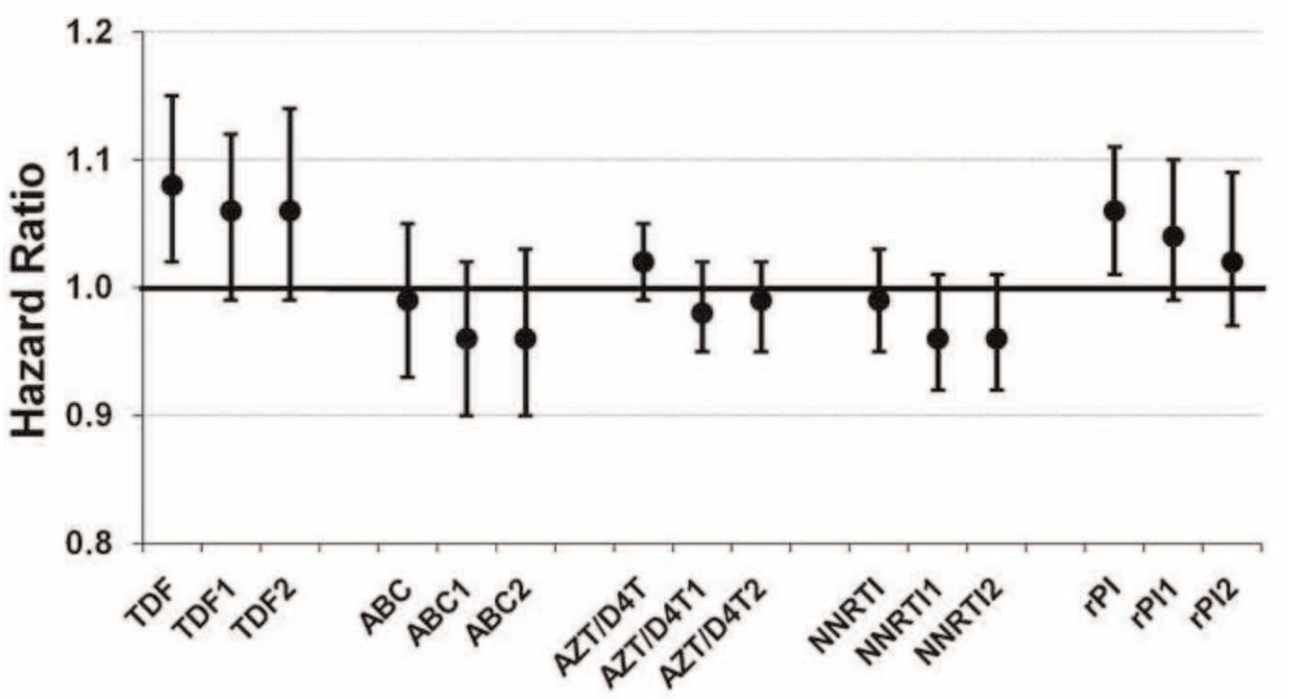

Fig. 1. Antiretroviral Exposure and Risk of Osteoporotic Fractures: 1988–2009. ABC, Abacavir; AZT/D4T, Zidovudine or Stavudine; NNRTI, Non-nucleoside reverse transcriptase inhibitors; rPI, ritonavir-boosted protease inhibitors; TDF, Tenofovir. Drug name followed by 1: Multivariate model 1; controlling for CKD, age, race, tobacco use, diabetes and BMI (MV Model 1); Drug name followed by 2: Multivariate model 2; controlling for Model 1 variables and concomitant exposure to other antiretrovirals.

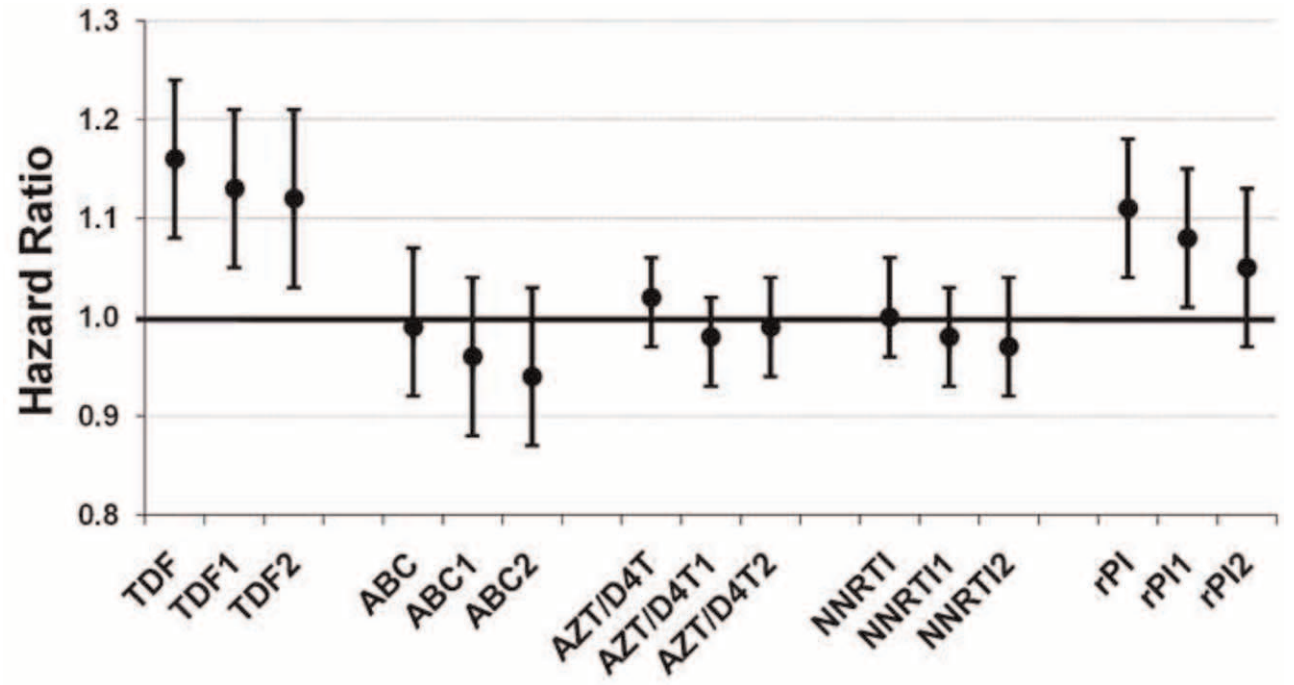

Fig. 2. Antiretroviral Exposure and Risk of Osteoporotic Fractures: 1996–2009. ABC, Abacavir; AZT/D4T, Zidovudine or Stavudine; NNRTI, Non-nucleoside reverse transcriptase inhibitors; rPI, ritonavir-boosted protease inhibitors; TDF, Tenofovir. Drug name followed by 1: Multivariate model 1; controlling for CKD, age, race, tobacco use, diabetes and BMI (MV Model 1); Drug name followed by 2: Multivariate model 2; controlling for Model 1 variables and concomitant exposure to other antiretrovirals.

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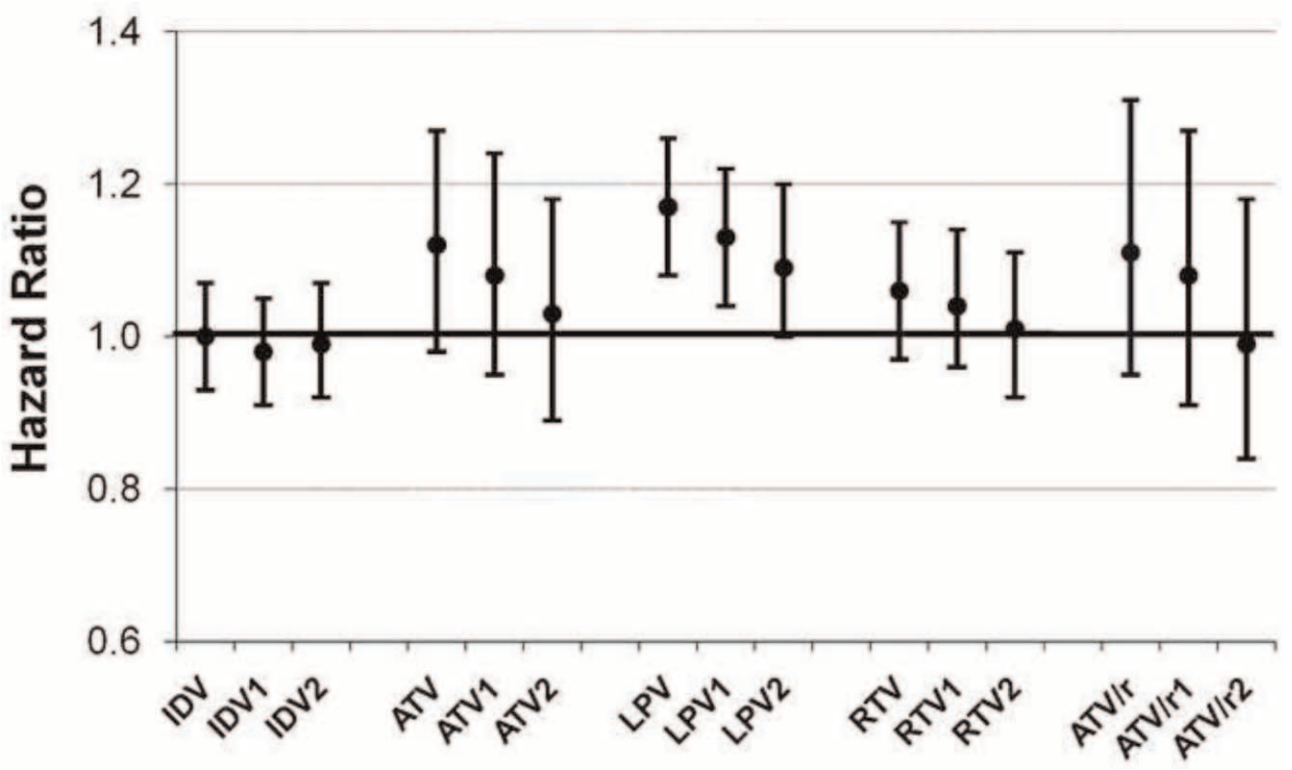

Fig. 3. Exposure to Specific Protease Inhibitors and Risk of Osteoporotic Fractures: HAART era (1996–2009). ATV, Atazanavir; ATV/r, ritonavir-boosted atazanavir; IDV, Indinavir; LPV, Lopinavir/Ritonavir; NFV, Nelfinavir; RTV, Ritonavir. Drug name followed by 1: Multivariate model 1; controlling for CKD, age, race, tobacco use, diabetes and BMI (MV Model 1); Drug name followed by 2: Multivariate model 2; controlling for Model 1 variables and concomitant exposure to other antiretrovirals.

initiation of antiretroviral therapy may also directly contribute to low bone mineral density [3,4,22,23].

Previous studies have suggested that antiretroviral drugs (ARVs) differ in their impact on bone health: TDF has been found to be associated with a greater decline in BMD than stavudine [10] or abacavir [11]. Antiretroviral regimens have also been shown to increase expression of markers of bone turnover. Our findings suggest for the first time that these ARV associations with either decreased BMD or increased bone turnover markers might be reflected in increased risk of OF. These findings, if confirmed, might warrant consideration of OF risk in decisions in ART initiation among HIV-infected patients. Hansen et al. [24] showed that in the HAART era, only HAART-exposed HIV patients had a higher risk of low-energy fractures than uninfected patients. Exposure to TDF was not independently predictive of higher fracture risk. However, unlike their analysis, we have been able to model cumulative exposure to TDF and other antiretrovirals prior to fracture events. We have also been able to adjust for concomitant exposure to other antiretroviral drugs.

Consistent with data from the general population OF were independently associated with advancing age, race other than Black, low BMI, and smoking in HIV-infected individuals. These traditional OF risk factors are much more important in predicting fracture risk among HIV-infected patients than ARV exposure. We did not find chronic kidney disease and diabetes to be independently associated with an increased risk of osteoporotic fractures after controlling for other risk factors, although both were significantly associated with increased fracture risk in the univariate analysis.

While we found significant increase in fracture rates in the HAART era, cumulative ARV may not entirely account for the HAART-to-pre-HAART eras increased risk. Greater fracture rates, higher (significant) HR for TDF and rPI in the HAART era could be due to longer survival, and exclusion of most patients with no ARV, mono, or dual ARV. Also, lower BMD was associated with controlled HIV replication in a recent study [19], and controlled viremia is much more likely in the HAART era.

With increased survival on highly active antiretroviral therapy and the aging of the HIV population, the morbidity and mortality related to non-AIDS related diseases is rapidly increasing, with cardiovascular disease (CVD) and liver disease (mostly HCV-related) being one of the most common causes of morbidity and mortality. Bone disease should be added to the list. Interventions

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used to mitigate that risk in the general population (calcium and vitamin D) have been showed to improve BMD of HIV-infected patients [25] and are advocated in HIV guidelines [26,27]. Future studies will need to determine whether these and/or changes in antiretroviral therapy will result in decreased risk of osteoporotic fractures. As a cautionary tale, recent data suggest that changes in BMD by such interventions are very poorly predictive of OF risk in the general population [28].

The strengths of our study include a large sample size (more than 56 000 patients) and high number of OF events (over 900), a uniform data collection on exposures and outcomes across VA system, and a long follow-up time including pre-HAART and HAART eras.

As limitations, ours is a retrospective cohort study. Osteoporotic fracture events were not ascertained (only ICD-9 code used – validated in other VA studies [6]. BMD was not evaluated and fractures cannot be proven to be osteoporotic in nature, however these, or similar definitions have been used in other epidemiological studies evaluating fracture risk [5,6,24]. Finally, as our study population is overwhelmingly male, the results might not be generalizable to women with HIV disease. Also, owing to the retrospective nature of the study, the associations observed are not necessarily causative. However, these findings suggest OF are an important cause of morbidity and mortality in HIV, and that while traditional OF risk factors are the most important contributors to the risk, further attention should be placed on antiretrovirals.

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Conflicts of interest

RB received research grants from Merck & Co, Tibotec Therapeutics, Bristol Myers Squibb and Abbott Pharmaceuticals. He also served as scientific advisor or consultant for EMD Serono, Merck & Co, Gilead, Tibotec Therapeutics and AIDS Arms; The other authors reports no relevant conflict of interest.

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