Overall benefit of antiretroviral treatment on the risk of fracture in HIV: nested casecontrol analysis in a health-insured population

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Objectives: Fractures are common and associated with multiple risk factors. We assessed the risks for fracture associated with time-dependent, differential antiretroviral drug exposures among a cohort of persons with human immunodeficiency virus (HIV) infection.

Design: Nested case-control study from an HIV cohort of 59,594 medically-insured persons with HIV infection enrolled in a medical care between January 1997 and March 2008.

Methods: Cases were subjects with a low-impact, non-traumatic fracture identified by ICD-9-CM codes; non-cases were 1:4 matched and without fracture.

Results: Cases comprised 2,411 persons with HIV infection with fractures who were risk-set matched to 9,144 persons with HIV infection without fractures. Exposure to antiretroviral (ARV) therapy by drug class and by duration (any drug/class) was associated with reduced risk for fracture. Drug-specific ARV exposures over time identified an increased risk for fracture associated with darunavir, delavirdine and saquinavir while reduced risk was associated with efavirenz, emtricitabine, lamivudine, tenofovir, and zidovudine. An initial null risk became a reduced risk with increased duration for nevirapine. In a similar pattern, abacavir, didanosine, nelfinavir, ritonavir and stavudine were initially associated with increased risk for fracture, after which the risk became null with increased duration of exposure. Null or uncertain risk for fracture was associated with amprenavir, atazanavir, enfuvirtide, fosamprenavir, indinavir, lopinavir, tipranavir, and zalcitabine.

Conclusions: ur findings suggest an overall reduced risk for facture in persons treated versus not treated with ARV drugs for HIV infection. Differential drug-specific exposure-response relationships for fracture will need to be further evaluated in other study populations.

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Introduction

The use of antiretroviral (ARV) treatment in human immunodeficiency virus (HIV) infection has clinical and economic benefits that offset potential untoward drug effects [1]. Associated risks for fracture and for reduced bone mineral density (BMD) among ARV-exposed individuals remain understudied and drug-specific risks have been inconsistent to date among persons with HIV infection [2–9]. Among ARV-naïve patients, reduced BMD of 2–6% has consistently been observed within the first year of exposure [2,9–12]. Loss of BMD has been reported among subjects randomized to continuous versus intermittent ARV therapy for HIV infection [8] ndependent of HIV infection, factors that influence risk prediction for fracture among persons with HIV infection include the traditional risks associated with reduced BMD such as aging, while drug-specific ARV exposures within combination regimens have not been fully explored [13–17]. Notably, educed BMD due to osteoporosis is

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asymptomatic and the most common adult clinical presentation of osteoporosis is a low-impact or non-traumatic fracture [2]. To date, quantifying the risk of fragility fractures has been best characterized in persons over 50 years of age [18]. Quantifying low-impact and non-traumatic fracture among persons with HIV infection is especially important given that changes in BMD are not necessarily unidirectional, acquired HIV infection often occurs prior to 50 years of age, and long-term survival with HIV infection necessitates combination ARV treatment. indings from studies of reduced BMD and ARV exposure have been inconsistent, and hence inconclusive, for drug-specific risks for facture among persons with HIV infection. We conducted a nested case-control study to assess risks for fracture in a health-insured population with HIV infection.

Methods

Study cohort

The cohort was comprised of 59,584 persons with HIV infection identified in the Ingenix Impact National Benchmark Database™ (INBD), an administrative claims database. The INBD is comprised of over 74 million members from the United States (US), and was previously called the Integrated Health Care Information System (IHCIS). The adults with HIV infection were continuously-enrolled, health-insured members for 12-plus months in INBD between January 1, 1997 and March 31, 2008, had pharmacy-claims eligibility, and evidence of one or more ICD-9-CM diagnostic code of 042 or v08 for HIV infection. The INBD database was de-identified by the vendor in compliance with the Health Insurance Portability and Accountability Act (HIPAA); no additional institutional review board approval was required.

Nested case-control: study design and population

During the 11.25-year study period, there were 2,477 subjects with fractures identified in the cohort. For the nested case-control study, full risk sets were explicitly constructed from the cohort with age as the primary time dimension using the RISKSET program module in OCMAP-Plus [19]. Risk sets were further reduced by matching on sex and on date of birth at age of fracture to control for cohort effects, and then combined into a single set with multiple cases when cases had the same event date. All subjects with incident fracture were included as cases. We randomly selected 4 non-case subjects from the full risk sets matching on gender, exact age, and year of birth (within 5 years). Time-dependent ARV exposure duration variables for cases and controls were computed as of the date of each event time at risk; in non-cases this was the date that the non-case reached the age of the corresponding case at time of fracture.

Subset analysis of abacavir versus tenofovir

In a subset analysis of persons exposed to abacavir versus tenofovir, the dataset was censored to the time interval from November 1, 2001 through March 31, 2008 to align with the post-approval, launch, and availability of each of the two drugs. Similar design, study definitions (for case, non-case, covariates, and outcome), and analyses were conducted for this subset analysis.

Study definitions

Date of birth was restricted to year of birth given vendor compliance with HIPAA; hence, subjects were each assigned July 15 for month/date to year of birth for the RISKSET program. Follow-up began on the first (index) date linked to an ICD-9-CM code for HIV infection. The enrollment interval prior to this index date was defined as surveillance and the time interval on and after this index date was defined as the study observation period. Severity of HIV infection was defined using criteria established for advanced HIV infection and for the acquired immune deficiency syndrome (AIDS) per the criteria established by the Centers for Disease Control and Prevention (CDC) [20].

Fracture, the primary study outcome, was defined by identification of the first ICD-9-CM code for closed, non-traumatic fracture in each subject's claim history during the study observation period; cases with more than one closed fracture code were individually assessed for potential trauma prior to inclusion as a case. Prior fracture was identified for each subject during the surveillance interval of INBD enrollment.

Prescription claims for drug exposure were identified by Uniform System of Classification Level 4 codes. Excess systemic glucocorticosteroid use was a bivariate response for a cumulative exposure to parenteral and oral glucocorticosteroid drugs equivalent to at least 675 mg of prednisone prior to either the date of fracture or the end of follow-up among subjects without fracture [21]. Exposure to either vitamin D or calcium supplementation was a combined variable in the univariate analysis and models. Duration of exposure measures for the specific ARV drugs were computed by restructuring the subject-level prescription history data for drug strength, metric quantity, and days supplied in order to quantify ARV drug class, differential ARV regimens, and drug-specific exposures.

The five categories of ARV drug classes were nucleoside reverse transcriptase inhibitors (NRTI), non-NRTI (NNRTI), protease inhibitors (PI), fusion inhibitors (FI), and entry inhibitors (EI). The duration of ARV exposure measures were further categorized qualitatively

(not exposed versus exposed) and quantitatively (in days) by ARV drug class and by each ARV drug.

Data analysis

We estimated odds ratios (OR) and 95% confidence intervals (CI) using exact conditional logistic regression programs in Stata (Stata, College Station, TX). The OR for each of the primary demographic, prescription history, and ARV exposure variables were also adjusted for potential confounding factors if warranted. All ARV drug exposure variables were categorized a priori into approximately equal exposure groups based on the distribution of fractures in an attempt to balance the precision of the risk estimates across subgroups. Multivariate models were adjusted for prior fracture, excess alcohol use, low physical activity, low body weight, hepatitis C virus (HCV) infection, excess steroid use, and treatment for osteoporosis with bisphosphonates. We assessed the statistical significance of each main effect (expressed as a global P-value) with a likelihood ratio statistic and conducted tests for linear trend (expressed as a trend P-value) using equally spaced scores.

Results

Study cohort

The study cohort comprised 59,584 persons with HIV infection enrolled in INBD over the 11.25-year study period. There were 30,405 persons (51.0%) who had one or more prescription claim for ARV therapy during the study period (Table 1). Antiretroviral treatment was more frequent among men, more common in the interval from 2003 through 2008 (71.8%) than from 1997 through 2002 (28.8%), and more frequent among subjects with advanced HIV infection, low body weight, lipodystrophy, hepatitis B virus (HBV) co-infection, and HCV co-infection.

Nested case-control study population and univariate risks for fracture

The final population for the nested case-control study consisted of 11,621 subjects, represented in 2,286 risk sets with 2,477 cases and 9,144 non-cases (Table 2). There were 157 risk sets with 2 cases, 15 risk sets with 3 cases, and one risk set with 5 cases. Risk for fracture was significantly higher, statistically, among subjects with prior fracture (OR 4.14, 95% CI 3.28–5.23; $p < 0.0001$), low physical activity (OR 2.15, 95% CI 1.74–2.67, $p < 0.0001$), excess alcohol use (OR 1.84, 95% CI 1.47–2.29. $p < 0.0001$), low body weight (OR 1.35, 95% CI 1.17–1.55, $p < 0.0001$), HCV co-infection (OR 1.28, 95% CI 1.09–1.49, $p = 0.002$), and advanced HIV infection defined as CDC category B (OR 1.24, 95% CI 1.09–1.40; $p = 0.001$) and CDC category C (OR 1.14, 95% CI 1.03–1.27; $p < 0.0001$). Risk for fracture was statistically significantly reduced among subjects exposed to ARV drugs (OR 0.64, 95% CI 0.58–0.71; $p < 0.0001$), with a similar exposure-response relationship identified for ARV drug class and for cumulative duration of exposure (Table 2).

Table 1. Demographic and clinical characteristics of 59,584 persons with HIV infection stratified by exposure to antiretroviral (ARV) drug treatment.

Variable	No ARV exposure[a] N = 29,179	ARV exposure[a] N = 30,405
Demographics		
Age: mean (SD)	38.7 (11.5)	41.9 (8.5)
Sex		
Male	16,919 (58.0)	25,689 (84.5)
Female	12,260 (42.0)	4,716 (15.5)
Geographic census region		
Northeast US	16,812 (57.6)	12,595 (41.4)
Other continental US	12,367 (42.4)	17,810 (58.6)
Year of enrollment		
1997-2002	9,634 (33.0)	8,743 (28.8)
2003-2008	19,545 (67.0)	21,662 (71.2)
Behavioral risks		
Excess alcohol use	754 (2.6)	752 (2.5)
Low physical activity	675 (2.3)	584 (1.9)
HIV-related conditions		
CDC category A	20,091 (69.2)	14,746 (48.5)
CDC category B	4,775 (16.4)	6,490 (21.3)
CDC category C	4,213 (14.4)	9,169 (30.2)
Comorbid conditions		
Prior fractures	984 (3.4)	198 (0.7)
Low body weight	1,263 (4.3)	3,462 (11.4)
Lipodystrophy	203 (0.7)	1,808 (6.0)
Hepatitis B virus	964 (3.3)	1,495 (4.9)
Hepatitis C virus	1,531 (5.3)	2,337 (7.7)
Prescription drug exposures[b]		
Proton pump inhibitor	3,731 (12.8)	4,903 (16.1)
Glucocorticosteroid excess[c]	1,631 (5.6)	1,669 (5.5)
Vitamin D/calcium	443 (1.5)	358 (1.2)
Bisphosphonates	485 (1.7)	303 (1.0)

US = United States, CDC = Centers for Disease Control and Prevention.
[a]Column data are in format of Number (%) unless otherwise denoted.
[b]One or more prescriptions in this category.
[c]Cumulative exposure of an equivalent to prednisone ≥675 mg.

Antiretroviral drug class-specific exposure-response relationships for fracture

Further analysis of ARV drug-specific exposure-response relationships revealed differential within-class risk estimates (Table 3). Reduced risk for fracture was associated with exposures to the NRTI and to the NNRTI drug classes, with a pattern of incremental reduction of risk with increased duration of exposure. Exposure to the PI drugs was associated with a null effect that became slightly reduced in the subset of subjects with the longest duration of exposure defined as 18 months or longer. Additionally, a null effect was noted for exposure to the FI in a small number of cases (N = 29) with fracture. There were no exposures to an EI drug among cases with fracture.

Antiretroviral drug-specific exposure-response relationships for fracture

Risk for fracture was further examined for ARV drug-specific exposures assessed by approximate quartiles of

Table 2. Univariate analysis of risk for fracture among 11,621 persons with HIV infection in a nested case-control study.

Descriptor	Case N = 2,477	Non-case N = 9,144	Odds ratio (95% conficence intervals)	Global p-value (Trend p-value)
Demographics				
Sex (female)	694	2,480	[a]	[a]
Geographic region (non-NE)	1,133	4,285	0.94 (0.86–1.03)	0.216
Enrollment year[a] (2003–2008)	1,714	6,388	0.95 (0.85–1.06)	0.328
Behavioral risks				
Excess alcohol use	124	258	1.84 (1.47–2.29)	<0.0001
Low physical activity	148	275	2.15 (1.74–2.67)	<0.0001
Comorbid conditions				
Prior fractures	163	168	4.14 (3.28–5.23)	<0.0001
Low body weight	315	891	1.35 (1.17–1.55)	<0.0001
Lipodystrophy	154	510	1.11 (0.92–1.34)	0.274
Hepatitis B virus	120	426	1.03 (0.83–1.27)	0.799
Hepatitis C virus	244	732	1.28 (1.09–1.49)	0.002
Prescription drug exposures				
Proton pump inhibitor	445	1,644	1.01 (0.89–1.13)	0.917
Glucocorticosteroid excess[b]	162	577	1.05 (0.88–1.26)	0.584
Vitamin D/Calcium	41	173	0.89 (0.63–1.26)	0.512
Bisphosphonate use	75	235	1.28 (0.97–1.70)	0.090
HIV-related				
Advanced HIV/AIDS				
Category B	423	1,358	1.24 (1.09–1.40)	0.001
Category C	598	2,049	1.14 (1.03–1.27)	<0.0001
ARV drug (Yes)	1,275	5,497	0.64 (0.58–0.71)	<0.0001
NRTI class	1,253	5,451	0.63 (0.57–0.70)	<0.0001
NNRTI class	649	3,294	0.61 (0.55–0.67)	<0.0001
PI class	786	3,184	0.85 (0.77–0.94)	0.0001
FI class	29	152	0.69 (0.46–1.03)	0.062
Duration of any ARV: months				
>0 -<12	680	2,586	0.73 (0.65–0.82)	<0.0001
12 - 24	325	1,474	0.62 (0.54–0.71)	<0.0001
>24	270	1,405	0.53 (0.46–0.62)	<0.0001

Non-NE = non-northeastern continental United States census regions.
[a]matching criteria.
[b]Cumulative exposure of an equivalent to prednisone ≥675 mg.

duration of exposure (in months) and subsequent categorization of exposure-response relationships grouped as risks that were increased, decreased, null, or uncertain (Table 4). Increased risk for fracture was noted for darunavir, delavirdine and saquinavir with each quartile of exposure. Reduced risk for fracture was consistently noted for efavirenz, emtricitabine, lamivudine, tenofovir, and zidovudine. An initial increased risk became protective with increased duration for nevirapine. In a similar pattern, didanosine, nelfinavir, ritonavir and stavudine were initially associated with a slightly increased point estimate of risk for fracture in the first quartile of exposure (shortest exposure), after which the risk became reduced with increased duration of exposure. Null or uncertain risk for fracture was associated with amprenavir, atazanavir, enfuvirtide, fosamprenavir, indinavir, lopinavir, tipranavir, and zalcitabine (Table 4).

Exposure-response relationships specific to abacavir versus tenofovir

To assess exposure-response relationships specific to abacavir and to tenofovir, a sub-analysis was restricted to the 8,879 cases and non-cases enrolled in care on or after November 1, 2001 (Table 5). Reduced risk for fracture was noted in unadjusted and adjusted models for subjects with ARV regimens inclusive of abacavir (OR 0.75, 95% CI 0.64–0.88), exclusive of abacavir (OR 0.61, 95% CI 0.54–0.69), inclusive of tenofovir (OR 0.63, 95% CI 0.55–0.72), and exclusive of tenofovir (OR 0.68, 95% CI 0.59–0.78). The estimates of risk for abacavir were slightly increased but not statistically significant among subjects with less than six months exposure (aOR 1.12, 95% CI 0.90–1.40) and with greater than 12 months exposure (aOR 1.17 95% CI 0.91–1.52), and reduced, but not statistically significant, for subjects with six to 12 months of exposure (aOR 0.87 95% CI 0.64–1.17). The estimates of risk for tenofovir were reduced, but not statistically significant, for subjects with less than six months exposure (aOR 0.92, 95% CI 0.76–1.10) and with six to 12 months of exposure (aOR 0.84, 95% CI 0.66–1.06), with slightly increased but not statistically significant risk for subjects with 12 or more months of exposure (aOR 1.08 95% CI 0.83–1.40).

Discussion

Our study identified an overall reduced risk for fracture in persons treated versus not treated with ARV drugs for

Table 3. Antiretroviral (ARV) drug class exposures (in months) and risk for fracture among 11,621 persons with HIV infection.

ARV drug class duration (months)	Case N = 2,477	Unadjusted Odds ratio[a] (95% confidence intervals)	Adjusted Odds ratio[a,b] (95% confidence intervals)
Nucleoside reverse transcriptase inhibitors (NRTI)			
>0-<4.5	319	0.82 (0.70–0.94)	0.83 (0.72–0.97)
4.5-<10.5	306	0.68 (0.58–0.78)	0.70 (0.61–0.82)
10.5-<20	304	0.63 (0.55–0.73)	0.64 (0.55–0.75)
20+	323	0.53 (0.46–0.61)	0.53 (0.46–0.61)
		$p^g \leq 0.0001$	$p^g \leq 0.0001$
		$p^t \leq 0.0001$	$p^t \leq 0.0001$
Non-nucleoside and non-nucleotide reverse transcriptase inhibitors (NNRTI)			
>0-<3	157	0.89 (0.74–1.08)	0.89 (0.74–1.08)
3-<8	166	0.85 (0.71–1.02)	0.87 (0.72–1.05)
8-<18	166	0.62 (0.52–0.74)	0.63 (0.53–0.75)
18+	160	0.57 (0.48–0.69)	0.59 (0.49–0.70)
		$p^g \leq 0.0001$	$p^g \leq 0.0001$
		$p^t \leq 0.0001$	$p^t \leq 0.0001$
Protease inhibitor			
>0-<4	211	0.97 (0.83–1.15)	0.99 (0.84–1.17)
4-<9	177	0.96 (0.80–1.14)	0.98 (0.82–1.17)
9-<18	195	0.96 (0.81–1.14)	0.97 (0.82–1.15)
18+	203	0.84 (0.71–0.99)	0.83 (0.70–0.99)
		$p^g = 0.344$	$p^g = 0.324$
		$p^t = 0.057$	$p^t = 0.070$
Fusion inhibitor			
exposed[c]	29	(0.66–1.51)	0.97 (0.64–1.48)
		$p^g = 0.990$	$p^g = 0.883$

No exposures to entry inhibitors.
[a]Unexposed participants used as baseline in all models.
[b]All models adjusted for prior fracture, excess alcohol use, low physical activity, low body weight, hepatitis C virus, excess glucocorticoid use, treatment of osteoporosis with bisphosphonates, and advanced HIV infection.
[c]Drugs with 30 or less exposed cases were dichotomized as unexposed/exposed.
[g]p = global p-value.
[t]p = trend p-value.

HIV infection. The study design and analysis highlights the complexity of estimating time-dependent, ARV drug-specific risks for fracture among persons on combination ARV regimens over different intervals of time for the treatment of HIVinfection [22]. Given the known dynamic complexity of bone metabolism in aging populations with HIV infection and differential ARV exposure, we emphasize three noteworthy findings from this nested case-control study.

First, exposures to ARV treatment by drug class, duration, and most drug-specific exposures were associated with reduced risk for fracture among persons with HIV infection. Second, beyond ARV drug class estimates of risk, the ARV drug-specific risk estimates for fracture revealed three different risk categories, with increased risk for fracture identified for three drugs (Table 4). For darunavir, although the number of fracture events were low, the estimate of risk was substantial (aOR 1.93, 95% CI 1.05–3.56; $p^g = 0.043$), and further assessment of this PI in other study populations seems justified. For delavirdine, the number of fracture events was low, the estimate of risk was moderate (aOR 1.59, 95% CI 0.94–2.71; $p^g = 0.095$), and future comparisons of risk in other populations may not be feasible given low prescribed use of delavirdine in current practice. For saquinivir, there were 115 exposed cases and although the approximate quartiles of risk varied, the global and trend values were consistent with increased risk. With two of these three drugs in the PI class, these data support some findings from two randomized trials that have identified an association of reduced BMD in the spine and PI exposures [11,12]. The potential correlations of reduced BMD short-term versus clinical benefits and risks of various PI-based regimens will require additional evaluation. Third, our time-censored subset analysis of abacavir versus tenofovir exposures revealed null risk in adjusted models for known risk variables and other ARV drug exposures (Table 5). Prior comparative analyses of abacavir versus tenofovir have been inconsistent, yet a significantly larger reduction in BMD has been consistently associated with tenofovir versus other NRTI agents [23–25]. Significant decreases in BMD were especially noted during the first year of exposure in patients randomized to abacavir/lamivudine and to tenofovir/emtricitabine, with either ritonavir-boosted atazanavir or efavirenz; reported fractures were all associated with trauma and not different between study arms [9].

Together, these drug-specific exposure-response relationships suggest an overall benefit of ARV treatment relative to estimates of risk for fracture in subjects without ARV treatment. While it is clinically relevant to discern distinctions in studies that assess changes in BMD versus fracture, our findings are consistent with several longitudinal studies of stable BMD in ARV-exposed

Table 4. Antiretroviral (ARV) drug specific exposures categorized by associations of risk for fracture in a nested case-control study of 11,621 persons with HIV infection.

Drug duration (months)	Case N = 2,477	Unadjusted odds ratio[a] (95% confidence intervals)	Adjusted OR[a,b] (95% confidence intervals)
Increased risk			
Darunavir[c] exposed	16	1.92 (1.05–3.52) $p^g = 0.043$	1.93 (1.05–3.56) $p^g = 0.043$
Delavirdine[c] exposed	20	1.55 (0.91–2.61) $p^g = 0.115$	1.59 (0.94–2.71) $p^g = 0.095$
Saquinavir			
>0-<3	34	1.81 (1.19–2.74)	1.93 (1.27–2.93)
3-<7	25	1.34 (0.84–2.14)	1.39 (0.87–2.23)
7-<15	31	1.76 (1.14–2.71)	1.81 (1.17–2.81)
15+	25	1.12 (0.72–1.76) $p^g = 0.006$, $p^t = 0.013$	1.15 (0.73–1.81) $p^g = 0.002$, $p^t = 0.008$
No effect or uncertain effect			
Abacavir			
>0-<3	105	1.05 (0.81–1.31)	1.06 (0.85–1.33)
3-<9	98	0.90 (0.71–1.13)	0.94 (0.74–1.18)
9-<20	91	0.76 (0.60–0.96)	0.76 (0.60–0.96)
20+	96	0.94 (0.74–1.18) $p^g = 0.155$, $p^t = 0.058$	0.96 (0.76–1.21) $p^g = 0.184$, $p^t = 0.107$
Amprenavir			
>0-<4	10	0.87 (0.43–1.74)	0.88 (0.44–1.77)
4-<9	12	1.09 (0.57–2.09)	1.06 (0.55–2.05)
9-<16	8	1.25 (0.56–2.79)	1.10 (0.49–2.48)
16+	9	1.05 (0.50–2.20) $p^g = 0.971$, $p^t = 0.704$	0.89 (0.42–1.88) $p^g = 0.988$, $p^t = 0.916$
Atazanavir			
>0-<2.5	52	1.04 (0.76–1.43)	1.07 (0.78–1.48)
2.5-<7	54	0.83 (0.61–1.12)	0.85 (0.63–1.16)
7-<17.5	52	0.72 (0.53–0.98)	0.74 (0.54–1.01)
17.5+	53	1.09 (0.80–1.50) $p^g = 0.157$, $p^t = 0.207$	1.13 (0.82–1.55) $p^g = 0.218$, $p^t = 0.351$
Didanosine			
>0-<3	62	1.19 (0.88–1.59)	1.20 (0.89–1.61)
3-<8	55	0.95 (0.70–1.29)	0.95 (0.70–1.29)
8-<15	53	0.96 (0.71–1.31)	0.97 (0.71–1.32)
15+	57	0.76 (0.57–1.02) $p^g = 0.282$, $p^t = 0.134$	0.75 (0.56–1.01) $p^g = 0.244$, $p^t = 0.125$
Enfuvirtide[c]			
Exposed	29	1.00 (0.66–1.51) $p^g = 0.990$	0.97 (0.64–1.48) $p^g = 0.883$
Fosamprenavir			
>0-<2	20	0.95 (0.58–1.57)	0.89 (0.54–1.47)
2-<6	24	1.06 (0.67–1.69)	1.02 (0.64–1.63)
6-<12	18	1.04 (0.61–1.77)	1.05 (0.62–1.80)
12+	17	0.91 (0.53–1.56) $p^g = 0.993$, $p^t = 0.919$	0.84 (0.49–1.45) $p^g = 0.957$, $p^t = 0.689$
Indinavir			
>0-<3	35	1.03 (0.70–1.52)	1.00 (0.67–1.48)
3-<8	33	1.06 (0.72–1.56)	1.05 (0.71–1.55)
8-<16	29	1.25 (0.81–1.91)	1.25 (0.81–1.93)
16+	33	1.05 (0.71–1.55) $p^g = 0.892$, $p^t = 0.433$	1.01 (0.68–1.51) $p^g = 0.902$, $p^t = 0.538$
Lopinavir			
>0-<3	66	0.81 (0.62–1.07)	0.82 (0.62–1.08)
3-<7	68	1.17 (0.88–1.54)	1.16 (0.88–1.54)
7-<14	72	1.02 (0.78–1.33)	0.99 (0.76–1.31)
14+	66	0.72 (0.55–0.95) $p^g = 0.054$, $p^t = 0.106$	0.70 (0.53–0.92) $p^g = 0.042$, $p^t = 0.067$
Nelfinavir			
>0-<2.5	42	1.13 (0.80–1.61)	1.15 (0.81–1.64)
2.5-<6	41	1.14 (0.80–1.64)	1.16 (0.81–1.66)
6-<16	41	0.73 (0.52–1.04)	0.75 (0.53–1.06)
16+	41	0.75 (0.53–1.05) $p^g = 0.121$, $p^t = 0.053$	0.78 (0.55–1.10) $p^g = 0.184$, $p^t = 0.101$
Ritonavir			
>0-<3	141	1.05 (0.86–1.28)	1.04 (0.85–1.27)
3-<7.5	130	1.05 (0.86–1.29)	1.06 (0.86–1.31)
7.5-<16	136	0.97 (0.80–1.18)	0.97 (0.79–1.18)
16+	134	0.83 (0.68–1.02)	0.83 (0.68–1.01)

Table 4 (*continued*)

Drug duration (months)	Case N = 2,477	Unadjusted odds ratio[a] (95% confidence intervals)	Adjusted OR[a,b] (95% confidence intervals)
		$p^g = 0.389$, $p^t = 0.183$	$p^g = 0.366$, $p^t = 0.177$
Stavudine			
>0-<3	85	1.36 (1.05–1.76)	1.38 (1.07–1.79)
3-<8	76	1.06 (0.82–1.38)	1.09 (0.84–1.42)
8-<16	70	0.93 (0.71–1.21)	0.94 (0.71–1.23)
16+	81	0.84 (0.66–1.08)	0.84 (0.65–1.08)
		$p^g = 0.090$, $p^t = 0.345$	$p^g = 0.068$, $p^t = 0.394$
Tipranavir[c]			
Exposed	10	1.05 (.51–2.16)	1.00 (0.49–2.07)
		$p^g = 0.891$	$p^g = 0.992$
Zalcitabine[c]			
Exposed	9	0.90 (.43–1.87)	0.94 (0.44–1396)
		$p^g = 0.769$	$p^g = 0.859$
Decreased Risk			
Efavirenz			
>0-<3	112	0.81 (0.65–0.99)	0.81 (0.65–1.00)
3-<8	117	0.84 (0.68–1.04)	0.85 (0.69–1.06)
8-<16	111	0.71 (0.57–0.87)	0.72 (0.58–0.89)
16+	119	0.55 (0.45–0.67)	0.55 (0.45–0.67)
		$p^g < 0.0001$, $p^t < 0.0001$	$p^g < 0.0001$, $p^t < 0.0001$
Emtricitabine			
>0-<3	86	0.84 (0.66–1.08)	0.82 (0.64–1.05)
3-<7	78	0.79 (0.61–1.01)	0.79 (0.62–1.03)
7-<12	81	0.90 (0.70–1.16)	0.94 (0.73–1.22)
12+	84	0.51 (0.40–0.65)	0.51 (0.40–0.65)
		$p^g < 0.0001$, $p^t < 0.0001$	$p^g < 0.0001$, $p^t < 0.0001$
Lamivudine			
>0-<3.5	219	0.95 (0.80–1.12)	0.97 (0.82–1.14)
3.5-<9	219	0.74 (0.63–0.86)	0.77 (0.66–0.91)
9-<19.5	227	0.70 (0.60–0.82)	0.71 (0.61–0.84)
19.5+	222	0.63 (0.54–0.74)	0.64 (0.55–0.75)
		$p^g < 0.0001$, $p^t < 0.0001$	$p^g < 0.0001$, $p^t < 0.0001$
Nevirapine			
>0-<2	56	1.60 (1.16–2.21)	1.60 (1.15–2.22)
2-<6	48	0.94 (0.68–1.30)	0.90 (0.65–1.25)
6-<17.5	50	0.56 (0.41–0.76)	0.57 (0.42–0.77)
17.5+	51	0.70 (0.52–0.95)	0.75 (0.55–1.02)
		$p^g < 0.0001$, $p^t = 0.0002$	$p^g < 0.0004$, $p^t = 0.0007$
Tenofovir			
>0-<3.5	135	0.82 (0.67–1.00)	0.83 (0.68–1.01)
3.5-<8	137	0.78 (0.64–0.95)	0.78 (0.64–0.96)
8-<17	146	0.66 (0.55–0.80)	0.68 (0.56–0.82)
17+	138	0.64 (0.53–0.78)	0.65 (0.53–0.79)
		$p^g < 0.0001$. $p^t < 0.0001$	$p^g < 0.0001$, $p^t < 0.0001$
Zidovudine			
>0-<3	153	0.99 (0.82–1.20)	0.98 (0.81–1.19)
3-<8	119	0.73 (0.59–0.90)	0.75 (0.61–0.93)
8-<19	129	0.61 (0.50–0.74)	0.62 (0.51–0.75)
19+	135	0.63 (0.52–0.76)	0.63 (0.52–0.77)
		$p^g < 0.0001$, $p^t < 0.0001$	$p^g < 0.0001$, $p^t < 0.0001$

[a]Unexposed participants used as baseline in all models.
[b]All models adjusted for prior fracture, excess alcohol use, low physical activity, low body weight, hepatitis C virus, excess glucocorticsteroid use, treatment of osteoporosis with bisphosphonates, and advanced HIV infection.
[c]Drugs with 30 or less exposed cases were dichotomized as unexposed/exposed.
[g]p = global p-value.
[t]p = trend p-value.

patients [5,7,25,26]. As BMD decreases with age, the mechanisms of bone modeling are not unidirectional and untreated HIV infection has been associated with uncoupled bone formation and bone resorption that seems attributed to both viral and inflammatory effects [27]. An undefined direct mechanism for bone remodeling is plausible in treated HIV infection and an indirect mechanism for bone remodeling is supported by lower levels of calcitrol (1,25-dihydroxyvitamin D) as reported in patients with advanced HIV infection compared to patients with early HIV infection [28]. Such changes in calcitrol may promote intestinal calcium absorption and regulation of osteoblast function. While there is theoretical biological plausibility that increased fat-free mass and decreased inflammation evident via changes in C reactive protein, interleukin-6, soluble tumor necrosis

Table 5. Risk assessment for fracture in persons with exposure to abacavir, tenofovir, and other ARV drugs for HIV infection enrolled in medical care between November 2001 and March 2008.

Drug	Case N = 1,854 No.	Unadjusted OR[a] (95% CI)	Adjusted OR[a,b] (95% CI)
ARV inclusive of abacavir	305	0.75 (0.64–0.88)	
ARV not inclusive of abacavir	641	0.61 (0.54–0.69)	
		$p^g < 0.0001$	––
ARV inclusive of tenofovir	498	0.63 (0.55–0.72)	
ARV not inclusive of tenofovir	448	0.68 (0.59–0.78)	
		$p^g < 0.0001$	––
No abacavir or tenofovir	271	0.64 (0.54–0.75)	0.80 (0.66–0.98)
Abacavir, no tenofovir	177	0.75 (0.62–0.91)	0.94 (0.76–1.16)
Tenofovir, no abacavir	370	0.59 (0.51–0.69)	0.81 (0.68–0.98)
Abacavir and tenofovir	128	0.76 (0.61–0.95)	0.95 (0.74–1.22)
		$p^g < 0.0001$	$p^g = 0.098$
Abacavir cumulative duration			
>0 to less than 6 months	130	1.12 (0.90–1.38)	1.12 (0.90–1.40)
6 to less than 12 months	61	0.83 (0.61–1.11)	0.87 (0.64–1.17)
>12 months	114	0.93 (0.75–1.17)	1.17 (0.91–1.52)
		$p^g = 0.356$, $p^t = 0.416$	$p^g = 0.303$, $p^t = 0.401$
Tenofovir cumulative duration			
>0 to less than 6 months	195	0.85 (0.72–1.02)	0.92 (0.76–1.10)
6 to less than 12 months	119	0.71 (0.57–0.87)	0.84 (0.66–1.06)
>12 months	184	0.67 (0.56–0.80)	1.08 (0.83–1.40)
		$p^g < 0.0001$, $p^t < 0.0001$	$p^g = 0.103$, $p^t = 0.162$

[a]Participants with no ARV exposure used as baseline in all models.
[b]All models adjusted for prior fracture, excess alcohol use, low physical activity, low body weight, hepatitis C virus, excess glucocorticosteroid use, treatment of osteoporosis with bisphosphonates, and advanced HIV infection.
[g]p = global p-value.
[t]p = trend p-value.

factor receptor (sTNFR) I and sTNFR II are linked to ARV treatment and altered BMD, such measures are beyond the scope of an observational database analysis [11,28,29].

As noted in a recent study by the HIV Outpatient Study investigators, our findings are consistent with several established risk factors for fracture [30–34]. Despite consistencies in established risks among numerous studies, reported exposure-response relationships for ARV treatment and fracture among persons with HIV infection have varied based on study design, execution, and analyses. Such distinctions are notable by population when restricted to either men or women, covariates such as age when assessed by year or by decade, and quantification of antiretroviral drug exposure when assessed as a dichotomous variable, drug class, or cumulative drug-specific exposure. As an example, a recent study among US women and a case-control study from Australia have each reported that tenofovir was not associated with fracture [31,34]. Given the inconsistencies in reported studies to date, additional investigations of exposure to protease inhibitors and to tenofovir remain important and clinically-relevant for future investigations.

We acknowledge several limitations associated with the report of these study findings. First, as a retrospective study executed with administrative claims data, ascertainment bias for both information and measurement exists inclusive of the assumption that a prescription claim equated with administration of the ARV drug as prescribed and the population is likely differential from randomized trial populations. We were unable to assess race (not available in INBD) or tobacco exposure (less than 5% identified in pre-study feasibility assessment), did not include a covariate for opiate use, testosterone use, or untreated hypogonadism, and likely underestimated the severity of advanced HIV infection or AIDS based on available CD4 counts and ICD-9-CM claims for opportunistic infections and malignancies. We were able to create claims-based variables for low body weight, low physical activity, and advanced HIV infection. Second, by design, we grouped all subjects with low-impact and non-traumatic fracture as cases and did not estimate risks specific for the lumbar spine, hip, and other bone. As such, we are not able to associate with findings with studies that have had BMD loss as the outcome of interest. Third, our study population was restricted to fractures in adults and the findings are not able to be generalized to children or to longitudinal changes in BMD [35]. Fourth, almost all subjects with ARV exposure in our study were on NRTI-containing regimens, and we are unable to expand upon findings from a recent report of greater changes in BMD for subjects randomized to NRTI-containing ARV regimens versus NRTI-sparing regimens [12]. Lastly, we were unable to assess ARV exposure prior to membership in the insured plan that was captured by INBD. It is nevertheless noteworthy that the study design, execution, and analysis combined the restructure of over 1.9 million ARV prescription claims using occupational epidemiology methods to estimate drug-specific exposure-response relationships.

In summary, bone fractures are common and risks for fracture seem multifactorial among persons with HIV infection. We report significantly reduced risk of fracture in a dichotomous analysis of ARV drug exposure, with a similar exposure-response relationship identified for ARV drug class and for cumulative duration of exposure. Differential ARV drug-specific risks for fracture suggest further assessment of individual drug exposures in other populations is warranted. Given the complexity of ARV treatment for long-term survival among aging populations with HIV infection, our findings contribute evidence to and support for future robust analysis of observational cohort data to assess and identify modifiable risk factors associated with aging and drug exposure-response relationships. Such comparative research efforts will be integral to optimizing incremental net health benefits with tailored ARV treatment in the years to come.

Acknowledgements

Conflicts of interest

None declared.

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