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Background

- As people with HIV (PWH) live longer through effective antiretroviral therapy (ART), certain conditions that are common in general population, including osteoporosis, can develop prematurely and are more prevalent in PWH.
- Infection with HIV is known to have an adverse impact on the likelihood of fracture risk.
- Both classical risk factors for osteoporosis and fracture and factors linked to HIV itself, such as inflammation, reconstitution syndrome, low CD4, and long-term use of ART may all play a role in decreased bone health in aging PWH.
- Use of tenofovir disoproxil fumarate (TDF) is associated with a lower bone mineral density (BMD) in PWH, but the relationship between use of tenofovir containing ART and incident fractures in PWH has not been well described.

Objectives

- Compare the incidence of fractures among PWH receiving tenofovir-containing ART and that among those used other ART regimens.
- Evaluate the association between receipt of tenofovir-containing ART and the risk of fracture, and identify other modifiable risk factors among PWH receiving ART.

Methods

Study design
- A retrospective cohort study.

Study period
- January 1, 2000 – December 31, 2016

Study setting
- Study sites: Kaiser Permanente (KP) in California (Northern California and Southern California) and Mid-Atlantic States (D.C., Maryland, Virginia).
- All sites are large integrated health systems providing comprehensive medical services to a total of over 12 million pre-paid health plan members.
- Evidence and guideline-based HIV care is provided in both specialty and primary care settings with greater uniformity among the three health systems.
- TDF was the primary tenofovir regimen used during the study period.

Study population
- Adult PWH (age ≥40 years) who received HIV care at the three health systems
- Who initiated a new ART regimen (ART-naïve or experienced) between January 1, 2000 - September 1, 2015.

Exclusion criteria
- Those with a history of dialysis, kidney transplant, metastatic cancer, or parathyroid abnormalities prior to ART initiation were excluded.

Methods

Index date and follow-up
- Index date: the date of the initiation of ART during the study period (defined as at least three antiretroviral agents separately or in combination).
- Follow-up: All PWH in the cohort were followed until the first occurrence of a fracture, death, membership disenrollment, or Dec 31, 2016 (the administrative end of the study).

Data Source
- The main data source is the KP Virtual Data Warehouse (VDW).
- The VDW is comprised of electronic health record- based datasets populated with linked demographics, administrative data, outpatient pharmacy, outpatient laboratory test results, and outpatient, inpatient and emergency room health care utilization data (including diagnoses) for all KP members.

Main Outcome
- Incident clinical fractures (ascertained by ICD-9 codes) following the initiation of ART (index date).

Main Predictor
- Initiation of tenofovir-containing ART at baseline --- including both TDF and tenofovir alafenamide (TAF), either taken individually or as part of a combination tablet formulation.

Covariates
- Sociodemographic characteristics at baseline: age, sex, race/ethnicity
- Clinical factors: baseline chronic comorbidities, baseline HIV viral load, and CD4 count (nadir and at start of first ART).
- Behavioral factors: history of smoking, alcohol use disorder, and drug use disorders.
- Other covariates: BMI (kg/m^2, prior to index date), abnormal eGFR (<60 ml/min/1.73m^2) , insurance type, study site.

Statistical Analysis
- Cox proportional hazards regression model was used to assess the adjusted hazard ratio (aHR) and 95% confidence intervals (CI) associated with tenofovir use and sociodemographic characteristics, clinical factors, substance use, adjusted for study site.

Results

- A total of 6,508 PWH (87% male) were included in the analysis, and about 52% were men who have sex with men.
- About 70.5% (n=4,585) PWH initiated tenofovir-containing ART (Table 1).
- The total follow-up time were 27,646 person-years (median: 3 person-years).
- There were 232 incident fractures identified among those who used TDF (IR:14.0 per 1,000 person-years, 95% CI: 13.9-14.2) and 128 fractures among those who did not use TDF (11.5 per 1,000 person-years, 95% CI: 11.3-11.7).
- The association between tenofovir use and fracture risk was not statistically significant (aHR 1.21, 95% CI: 0.93-1.57), after adjustment for age, sex, race/ethnicity, BMI, CD4 count, HIV virus load, history of chronic liver disease, diabetes, eGFR, smoking, alcohol use disorder, and substance use disorder.
- Other significant risk factors for fractures included age, history of chronic liver diseases, history of smoking, alcohol use disorder, and drug use disorder (Figure 1).
- BMI (ever >=30 kg/m^2), diabetes, CD4 nadir, HIV viral load, and abnormal eGFR were not associated with fracture risk in multivariable analysis.

Discussion

- Our results show majority of PWH had received tenofovir (primarily TDF) across three health systems.
- PWH who received tenofovir-containing ART were more likely to experience fractures than those who received other regimens; however, the association was not statistically significant.
- In multivariable analyses, among the clinical factors studied, chronic liver disease was associated with a 38% greater risk of fracture.
- The observed associations between smoking and substance use disorders and the increased risk of fracture are consistent with existing evidence that links nicotine and substance abuse with bone loss in both men and women.

Limitations

- Follow-up and data collection ended in 2016 --- it is possible that different results may have been found with more recent increased use of TAF.
- We cannot rule out residual confounding, and there may be inadequate statistical power to detect .
- Our study cohort was based among insured adults receiving care in integrated health systems, which may affect generalizability to other populations without access to care.

Conclusions

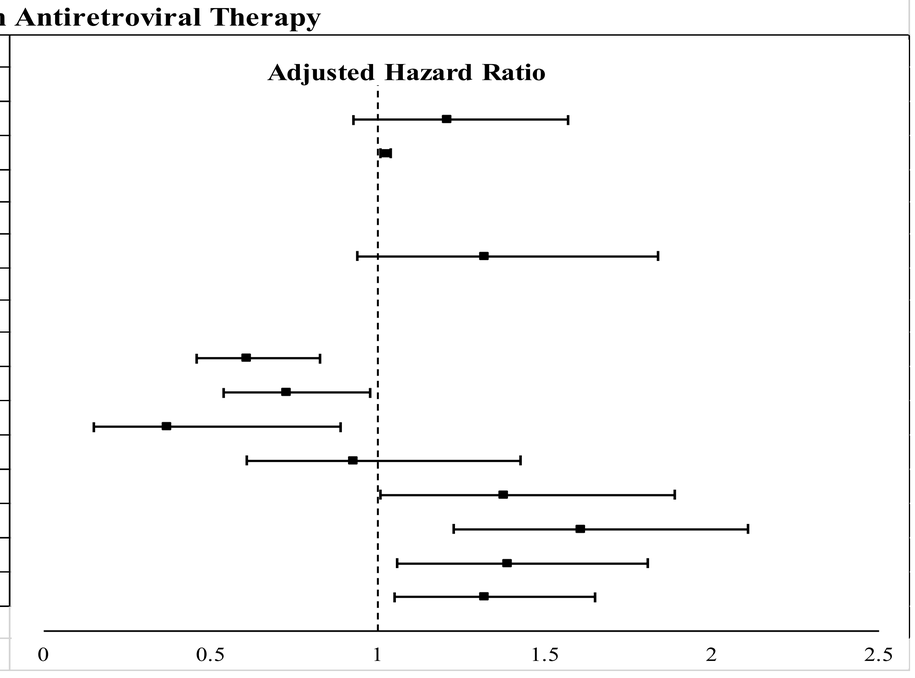
- Use of tenofovir-containing ART was not significantly associated with increased risk of fractures among PWH.
- To reduce the burden of fractures, healthcare providers and PWH should address key modifiable risk factors, including screening and treating heavy alcohol and drug use, smoking cessation, and treating chronic liver diseases.

Table 1. Baseline demographic characteristics.

Characteristics	With tenofovir use	Without tenofovir use	P-value
N	4,585	1,923	
Sex, n (%)			<0.01
Male	3,972 (86.6)	1,717 (89.3)	
Female	613 (13.4)	206 (10.7)	
Age, years			0.01
Median (IQR)	47.8 (44.0, 53.1)	47.2 (43.3, 53.2)	
Race/ethnicity			<0.01
White	1,907 (41.6)	817 (42.5)	
Black	1,127 (24.6)	386 (20.1)	
Hispanic	922 (20.1)	362 (18.8)	
Asian	169 (3.7)	58 (3.0)	
Other/Unknown	460 (10.0)	300 (15.6)	

Figure 1. Predictors of Fractures among PWH on Antiretroviral Therapy

Risk Factors	aHR (95% CI)
Tenofovir use at baseline	1.21 (0.93-1.57)
Age	1.03 (1.01-1.04)
Gender	
Male	Reference
Female	1.32 (0.94-1.84)
Race/Ethnicity	
non-Hispanic White	Reference
non-Hispanic Black	0.61 (0.46- 0.83)
Hispanic	0.73 (0.54-0.98)
Asian	0.37 (0.15-0.89)
Other/Unknown	0.93 (0.61-1.43)
Chronic Liver Diseases	1.38 (1.01-1.89)
History of alcohol use disorder	1.61 (1.23-2.11)
History of drug use disorder	1.39 (1.06-1.81)
History of smoking	1.32 (1.05-1.65)



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