

A Retrospective Analysis of Bone Loss in Emtricitabine-Tenofovir Therapy for HIV PrEP

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Introduction

- Tenofovir Disoproxil Fumarate – Emtricitabine (TDF-FTC), a commonly prescribed medication for pre-exposure prophylaxis (PrEP), is associated with a reduced risk of HIV infection.
- Clinical trials have shown that once daily oral PrEP with TDF-FTC reduces the risk of HIV infection in heterosexual men, transgender women, men who have sex with men, and people who inject drugs¹⁻⁵
- There is conflicting evidence on whether or not TDF-FTC, along with the initiation of other types of anti-retroviral therapy is associated with a reduction in bone mineral density⁶⁻⁹
- Is the risk of osteopenia/osteoporosis a dose dependent phenomenon?

Objectives

- To address the risk of osteopenia or osteoporosis in a real life setting for patients on TDF-FTC therapy for PrEP
- To address the breakthrough incidence of HIV in patients with relation to TDF-FTC adherence

Study Definitions

- Osteopenia/osteoporosis: DEXA scan T-score of ≤ -1
- Proportion of Days Covered (PDC), a measure of adherence: $\frac{\# \text{ of days supply}}{\# \text{ of follow-up days}} \times 100\%$

Inclusion Criteria

- Kaiser Permanente Southern California members with at least 1 year of membership before the most recent treatment episode
- Patients of 18 years of age or older on TDF-FTC therapy for PrEP between 2012 and 2020 with no prior history of bone loss
- Must have DEXA scan during the study period

Exclusion Criteria

- Patients who were HIV positive prior to therapy
- Pregnant patients
- Patients on TDF-FTC for reasons besides PrEP
- Patients with history of T-score ≤ -1

Methods

- IRB approved retrospective cohort study (N = 7,698)
- Patient charts dated from January 2012 to December 2020 were extracted and reviewed using EPIC/Health Connect electronic medical record system at Kaiser Permanente
- PDC is measured from the index date(start date of most recent PrEP episode until patient is censored/eg, death, disenrollment, end of study period, occurrence of osteopenia/osteoporosis, or until the end of the current PrEP episode (plus 60 days), whichever comes first.
- Age, sex, race, HIV status, T-scores from DEXA scan, proportion of days covered, diagnosis of hepatitis B, C, diabetes mellitus, cardiovascular disease, chronic kidney disease, and hypertension, baseline eGFR level, and body mass index (BMI) were extracted from the electronic health records
- Osteopenia/osteoporosis was defined as any T-score ≤ -1 during the follow-up period. Descriptive statistics was used to compare patient characteristics between those with and without osteoporosis/osteopenia during follow-up.
- Time to the first incidence of osteoporosis/osteopenia was modeled using a Cox proportional hazards model, with PDC and other baseline patient characteristics included as covariates.
- ICD 9/10 diagnosis and chart review were used to detect new incidence of HIV infection

Highlights

- High adherence to TDF-FTC (90% and greater) was significantly associated with an increase in the incidence of osteoporosis and osteopenia
- TDF-FTC confers high protection against HIV infection
- Counseling on the incidence of osteoporosis/osteopenia and routine screening should be conducted on patients initiated on TDF-FTC
- Future studies should explore the utilization of on-demand TDF-FTC therapy for PrEP in lieu of continuous therapy to potentially mitigate the risk of serious adverse effects

Table 1. Summary of patient factors in patients with normal bone mineral density versus osteopenia or osteoporosis.

Category	T-score ≥ 1 (any osteopenia or osteoporosis)		p-value
	(N = 7,811)	(N = 1,171)	
Length of follow-up (days) ^a	7481	2,117	<0.0001
Mean (SD)	503.0 (281.3)	581.1 (275.7)	
Median	309	341	
Q1, Q3	111, 885	462, 1044	
Range	(11,266-626)	(1,6-3122)	
PDC (%)	7481	2,117	<0.0001
Mean (SD)	78.4 (20.3)	96.2 (8.2)	
Median	81	93	
Q1, Q3	63, 96	86, 100	
Range	(67,180-90)	(61,100-90)	
PDC (%) category			<0.0001
<90%	2584 (345.3%)	197 (96.8%)	
90-99%	4527 (604.7%)	29 (1.2%)	
Age groups			<0.0001
18-29	1668 (15.6%)	41 (1.9%)	
30-39	1901 (25.7%)	71 (3.2%)	
40-49	1322 (17.7%)	31 (1.4%)	
50+	850 (11.4%)	17 (0.8%)	
Sex			0.042
Female	233 (3.1%)	2 (0.1%)	
Male	7248 (96.9%)	211 (99.9%)	
Race/ethnicity			<0.0001
Asian	2462 (33.0%)	131 (62.2%)	
Hispanic	1901 (25.7%)	41 (1.9%)	
White	1781 (23.8%)	21 (1.0%)	
Black	138 (1.8%)	5 (0.2%)	
Others or unknown	428 (5.7%)	9 (0.4%)	
History of hepatitis B			<0.0001
No	52 (0.7%)	6 (0.3%)	
Yes	84 (1.1%)	2 (0.1%)	
History of hepatitis C			0.781
No	407 (5.4%)	19 (0.9%)	
Yes	310 (4.1%)	27 (1.2%)	
History of diabetes			<0.0001
No	440 (5.9%)	23 (1.1%)	
Yes	977 (13.1%)	45 (2.1%)	
History of CKD			<0.0001
No	345 (4.6%)	29 (1.4%)	
Yes	170 (2.3%)	9 (0.4%)	
History of hypertension			<0.0001
No	303 (4.0%)	6 (0.3%)	
Yes	305 (4.1%)	6 (0.3%)	
BMI category ^b			<0.0001
Normal weight	2498 (33.5%)	73 (3.5%)	
Overweight	2377 (32.1%)	101 (4.7%)	
Obese	1315 (17.5%)	77 (3.7%)	
Other	373 (5.0%)	11 (0.5%)	

a. Length of follow-up is based on the date of the most recent TDF-FTC episode until the occurrence of the event of interest (i.e., osteopenia or osteoporosis), death, disenrollment, end of study, or until the end of the 10-year observation period. b. BMI category was defined as follows: normal weight, BMI < 25.0; overweight, BMI 25.0-29.9; obese, BMI 30.0-34.9; other, BMI ≥ 35.0 .

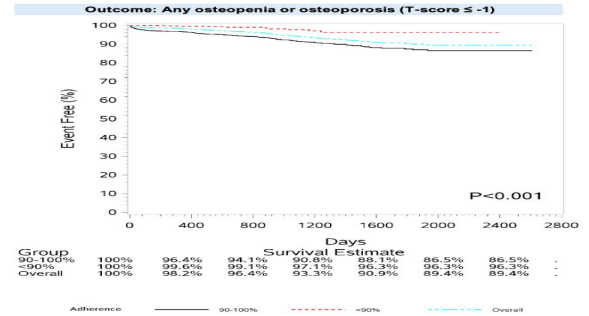
Table 2. Survival analysis of T-score ≤ -1 during follow-up for patients with any osteopenia or osteoporosis.

Category	T-score ≤ -1 (any osteopenia or osteoporosis)		p-value
	Unadjusted HR	Adjusted HR	
PDC (%) category			<0.0001
<90%	8.18 (5.12, 13.08)	5.34 (3.34, 8.41)	
90-99%	reference	reference	
Age groups			<0.0001
18-29	0.012 (0.005, 0.023)	0.01 (0.005, 0.021)	
30-39	0.017 (0.008, 0.035)	0.02 (0.01, 0.05)	
40-49	0.137 (0.069, 0.267)	0.12 (0.06, 0.25)	
50+	reference	reference	
Sex			0.424 (0.105, 1.768)
Female	0.424 (0.105, 1.768)	0.79 (0.18, 3.08)	
Male	reference	reference	
Race/ethnicity			<0.0001
Asian	reference	reference	
Asian/Pacific Islander	1.554 (0.95, 0.87)	1.4 (0.81, 2.24)	
Black	0.236 (0.097, 0.577)	0.48 (0.19, 1.17)	
Hispanic	1.038 (0.26, 4.15)	1.03 (0.15, 1.48)	
Others or unknown	0.649 (0.249, 0.942)	0.97 (0.49, 1.92)	
History of hepatitis B			<0.0001
No	reference	reference	
Yes	2.591 (1.15, 5.83)	1.42 (0.62, 3.26)	
History of hepatitis C			<0.0001
No	0.767 (0.191, 3.08)	0.64 (0.16, 2.61)	
Yes	reference	reference	
History of diabetes			<0.0001
No	reference	reference	
Yes	1.577 (0.96, 2.482)	0.83 (0.51, 1.41)	
History of CKD			<0.0001
No	reference	reference	
Yes	3.134 (1.694, 6.61)	1.21 (0.79, 1.84)	
History of CKD			<0.0001
No	reference	reference	
Yes	1.885 (1.283, 2.901)	1.13 (0.79, 1.64)	
History of hypertension			<0.0001
No	reference	reference	
Yes	2.312 (1.646, 3.261)	0.82 (0.41, 1.13)	
Baseline eGFR			<0.0001
< 30 mL/min/1.73 m ²	3.291 (2.149, 5.079)	0.69 (0.45, 1.08)	
30-59 mL/min/1.73 m ²	3.593 (2.062, 6.586)	0.78 (0.19, 1.25)	
> 60 mL/min/1.73 m ²	reference	reference	
Other	1.081 (0.472, 2.475)	0.60 (0.37, 2.01)	
BMI category (last 12 months)			<0.0001
Underweight	0.607 (0.064, 4.373)	3.95 (0.31, 31.60)	
Normal weight	reference	reference	
Overweight	1.225 (0.671, 6.54)	0.82 (0.28, 2.2)	
Obese	0.614 (0.415, 0.912)	0.61 (0.26, 0.86)	
Other	0.371 (0.112, 1.18)	0.2 (0.02, 1.09)	

Note. HR, hazard ratio; CI, confidence interval. Adjusted values controlled for age, sex, race/ethnicity, history of hepatitis B, history of hepatitis C, history of diabetes, history of CKD, history of hypertension, history of osteopenia/osteoporosis, baseline eGFR, and BMI.

Results

Figure 1. Kaplan-Meier graph, overall and stratified by percentage of days covered (PDC).



Note: p-value was calculated using the log-rank test.

- Of 7,698 patients, 217 developed osteopenia or osteoporosis (T-score ≤ -1)
- Average follow-up time for the cohort is 502.6 days
- Patients in a PDC category of 90-100% (90.8%) were more likely to develop osteopenia/osteoporosis compared to patients in a PDC category below 90% (9.2%) (p<0.001)
- Kaplan-Meier curve demonstrated a significant decrease in event-free rate of any osteopenia or osteoporosis development in 6.5 years after the start of the most recent TDF-FTC episode in patients with PDC of 90-100% (86.5%) vs. PDC <90% (96.3%) (p<0.001) (Figure 1)
- Unadjusted survival analysis showed significantly higher hazard ratios for the risk of osteopenia/osteoporosis in patients with PDC 90-100%, Hep B, CVD, CKD, HTN, and baseline eGFR < 90 mL/min/1.73 m² (Table 1). When adjusted for all covariates, the adjusted HR only showed patients with PDC 90-100% to be at significant risk for osteopenia/osteoporosis (Table 2)
- No incidence of HIV infection was detected in the sample population

Conclusion

- A correlative relationship between TDF-FTC adherence and incidence of osteopenia/osteopenia was observed
- Hepatitis B, CVD, CKD, age, baseline eGFR<90 mL/min/1.73 m² and BMI were not associated with an increase in the risk of osteopenia/osteopenia after adjusting for other confounders
- Obesity conveyed a protective effect on the incidence of osteoporosis/osteopenia
- This study was able to confirm that TDF-FTC is highly effective against HIV infection even with low adherence rate patients

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Disclosures

There are no disclosures on behalf of all the authors.

