

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

Joseph C. Chang, Pharm.D.,BCSCP; Duy Do, PhD.; Hector Delgado, Pharm.D., APH; An Huynh, Pharm.D. Candidate 2023; Natalie Kanimian, Pharm.D. Candidate 2022;

## 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 drugs<sup>1-5</sup>
- 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 density<sup>6-9</sup>
- 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  $\leq -1$
- 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  $\leq -1$

## 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  $\leq -1$  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 $\geq 1$ (any osteopenia or osteoporosis) |               | p-value |
|---|---|---------------|---------|
|   | N = 7,811   | N = 2,173     |         |
| Length of follow-up (days) <sup>a</sup> | 7481  | 2,117         | <0.0001 |
| Mean (SD)                               | 503.0 (281.3)                                     | 581.1 (275.7) |         |
| Median                                  | 309   | 341           |         |
| Q1, Q3                                  | 111, 616  | 402, 1,044    |         |
| Range                                   | 11,126,626  | 1,16,192,12   |         |
| PDC (%)                                 | 7481  | 2,117         | <0.0001 |
| Mean (SD)                               | 78.4 (20.3)                                       | 96.2 (8.2)    |         |
| Median                                  | 91  | 93            |         |
| Q1, Q3                                  | 63, 96  | 96.2, 100.0   |         |
| Range                                   | 0.7, 100.0  | 0.1, 100.0    |         |
| PDC (%) category                        | 2,584 (34.5%)                                     | 197 (9.2%)    | <0.0001 |
| <90%                                    | 1,571 (60.9%)                                     | 29 (2.2%)     |         |
| Age groups                              | 3,668 (15.6%)                                     | 417 (9%)      | <0.0001 |
| 18-29                                   | 1,015 (8.7%)                                      | 71 (7.2%)     |         |
| 30-39                                   | 1,322 (17.7%)                                     | 131 (14.1%)   |         |
| 40-49                                   | 850 (14.9%)                                       | 171 (19.8%)   |         |
| 50+                                     | 381 (3.3%)  | 24 (2.9%)     | 0.042   |
| Sex                                     | 7,048 (96.9%)                                     | 2,119 (97.6%) | <0.0001 |
| Male                                    | 6,462 (15.6%)                                     | 1,713 (22.2%) |         |
| Female                                  | 596 (4.1%)  | 41 (2.3%)     |         |
| Race/ethnicity                          | 7,811   | 2,173         | <0.0001 |
| Asian/Pacific Islander                  | 1,781 (15.2%)                                     | 21 (2.7%)     |         |
| Black                                   | 1,318 (10.7%)                                     | 52 (2.7%)     |         |
| Others or unknown                       | 4,712 (43.7%)                                     | 914 (41.6%)   |         |
| History of hepatitis B                  | 52 (0.7%)   | 6 (0.3%)      | 0.0005  |
| No                                      | 84 (1.1%)   | 2 (0.1%)      | 0.781   |
| Yes                                     | 407 (8.9%)  | 19 (0.9%)     | 0.0002  |
| History of diabetes                     | 310 (4.3%)  | 27 (1.2%)     | <0.0001 |
| No                                      | 440 (5.9%)  | 23 (0.8%)     | 0.004   |
| Yes                                     | 977 (13.1%)                                       | 45 (2.0%)     | <0.0001 |
| History of hypertension                 | 345 (4.6%)  | 29 (1.3%)     | <0.0001 |
| No                                      | 170 (2.3%)  | 99 (4.5%)     | 0.0002  |
| Yes                                     | 910 (9.7%)  | 41 (2.7%)     | <0.0001 |
| BMI category                            | 7,617   | 1,870         | <0.0001 |
| Normal weight                           | 2,498 (15.4%)                                     | 71 (3.8%)     |         |
| Overweight                              | 2,877 (18.4%)                                     | 101 (5.4%)    |         |
| Obese                                   | 1,935 (12.9%)                                     | 77 (4.1%)     |         |
| Unknown                                 | 317 (2.1%)  | 11 (0.6%)     |         |

a. Length of follow-up is based on the date when the patient was initiated on TDF-FTC therapy until the occurrence of the event or the end of the 107,737 person-years study. Missing data were excluded. b. Missing data were excluded. c. Missing data were excluded. d. Missing data were excluded. e. Missing data were excluded. f. Missing data were excluded. g. Missing data were excluded. h. Missing data were excluded. i. Missing data were excluded. j. Missing data were excluded. k. Missing data were excluded. l. Missing data were excluded. m. Missing data were excluded. n. Missing data were excluded. o. Missing data were excluded. p. Missing data were excluded. q. Missing data were excluded. r. Missing data were excluded. s. Missing data were excluded. t. Missing data were excluded. u. Missing data were excluded. v. Missing data were excluded. w. Missing data were excluded. x. Missing data were excluded. y. Missing data were excluded. z. Missing data were excluded. AA. 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Table 2. Survival analysis of T-score  $\leq -1$  during follow-up for patients with any osteopenia or osteoporosis.

| Category                         | T-score $\leq -1$ (any osteopenia or osteoporosis) |                    | p-value              |
|----------------------------------|--|--------------------|----------------------|
|                                  | Unadjusted HR                                      | Adjusted HR        |                      |
| PDC (%) category                 | 90-100%  | 100% CI            | <0.0001              |
| <90%                             | 8.18 (5.12, 13.08)                                 | 5.34 (3.34, 8.41)  |                      |
| Age groups                       | 18-29  | reference          | 0.002 (0.005, 0.013) |
| 30-39                            | 0.017 (0.008, 0.035)                               | 0.02 (0.01, 0.05)  | 0.0001               |
| 40-49                            | 0.137 (0.095, 0.197)                               | 0.12 (0.08, 0.179) | 0.0001               |
| 50+                              | reference  | reference          | reference            |
| Sex                              | Female   | reference          | 0.424 (0.105, 1.768) |
| Male                             | reference  | 0.79 (0.18, 3.09)  | 0.0001               |
| Race/ethnicity                   | Asian  | reference          | 1.48 (0.2, 2.24)     |
| Black                            | 0.236 (0.097, 0.577)                               | 0.48 (0.19, 1.17)  | 0.0001               |
| Others or unknown                | 1.038 (0.26, 4.13)                                 | 1.03 (0.15, 1.48)  | 0.0001               |
| History of hepatitis B           | No   | reference          | 0.97 (0.49, 1.92)    |
| Yes                              | 2.591 (1.15, 5.891)                                | 1.42 (0.42, 3.26)  | 0.0001               |
| History of diabetes              | No   | reference          | 0.767 (0.191, 3.086) |
| Yes                              | 0.64 (0.16, 2.41)                                  | 0.64 (0.16, 2.41)  | 0.0001               |
| History of hypertension          | No   | reference          | 1.577 (0.96, 2.482)  |
| Yes                              | 0.83 (0.51, 1.41)                                  | 0.83 (0.51, 1.41)  | 0.0001               |
| History of CKD                   | No   | reference          | 1.13 (0.79, 1.64)    |
| Yes                              | 3.134 (1.694, 6.49)                                | 1.21 (0.79, 1.84)  | 0.0001               |
| History of CKD                   | No   | reference          | 1.885 (1.225, 2.901) |
| Yes                              | 1.13 (0.79, 1.64)                                  | 1.13 (0.79, 1.64)  | 0.0001               |
| History of hypertension          | No   | reference          | 0.82 (0.41, 1.13)    |
| Yes                              | 2.312 (1.686, 3.161)                               | 0.82 (0.41, 1.13)  | 0.0001               |
| Baseline eGFR                    | < 30 mL/min/1.73 m <sup>2</sup>                    | reference          | 3.291 (2.149, 5.079) |
| 30-59 mL/min/1.73 m <sup>2</sup> | 0.59 (0.382, 0.898)                                | 0.59 (0.38, 0.898) | 0.0001               |
| > 60 mL/min/1.73 m <sup>2</sup>  | 0.86 (0.475, 0.912)                                | 0.86 (0.25, 2.01)  | 0.0001               |
| Unknown                          | 1.081 (0.472, 2.473)                               | 0.86 (0.25, 2.01)  | 0.0001               |
| BMI category (last 12 months)    | Underweight  | reference          | 0.607 (0.064, 4.373) |
| Normal weight                    | 0.607 (0.064, 4.373)                               | 3.95 (0.31, 51.60) | 0.0001               |
| Overweight                       | 1.225 (0.671, 6.54)                                | 0.82 (0.26, 2.2)   | 0.0001               |
| Obese                            | 0.614 (0.415, 0.912)                               | 0.61 (0.25, 0.86)  | 0.0001               |
| Unknown                          | 0.371 (0.112, 1.182)                               | 0.32 (0.1, 1.09)   | 0.0001               |

HR, hazard ratio; CI, confidence interval. Adjusted values controlled for age, sex, race/ethnicity, history of hepatitis B, diabetes, hypertension, CKD, osteopenia, baseline eGFR, and BMI.   
 a. Missing data were excluded. b. Missing data were excluded. c. Missing data were excluded. d. Missing data were excluded. e. Missing data were excluded. f. Missing data were excluded. g. Missing data were excluded. h. Missing data were excluded. i. Missing data were excluded. j. Missing data were excluded. k. Missing data were excluded. l. Missing data were excluded. m. Missing data were excluded. n. Missing data were excluded. o. Missing data were excluded. p. Missing data were excluded. q. Missing data were excluded. r. Missing data were excluded. s. Missing data were excluded. t. Missing data were excluded. u. Missing data were excluded. v. Missing data were excluded. w. Missing data were excluded. x. Missing data were excluded. y. Missing data were excluded. z. Missing data were excluded. AA. Missing data were excluded. AB. Missing data were excluded. AC. Missing data were excluded. AD. Missing data were excluded. AE. Missing data were excluded. AF. Missing data were excluded. AG. Missing data were excluded. AH. Missing data were excluded. AI. Missing data were excluded. AJ. Missing data were excluded. AK. Missing data were excluded. AL. Missing data were excluded. AM. Missing data were excluded. AN. Missing data were excluded. AO. Missing data were excluded. AP. Missing data were excluded. AQ. Missing data were excluded. AR. Missing data were excluded. AS. Missing data were excluded. AT. Missing data were excluded. AU. Missing data were excluded. AV. Missing data were excluded. AV. Missing data were excluded. AW. Missing data were excluded. AX. Missing data were excluded. AY. Missing data were excluded. AZ. Missing data were excluded. BA. Missing data were excluded. BB. Missing data were excluded. BC. Missing data were excluded. BD. Missing data were excluded. BE. Missing data were excluded. BF. Missing data were excluded. BG. Missing data were excluded. BH. Missing data were excluded. BI. Missing data were excluded. BJ. Missing data were excluded. BK. Missing data were excluded. BL. Missing data were excluded. BM. Missing data were excluded. BN. Missing data were excluded. BO. Missing data were excluded. BP. Missing data were excluded. BQ. Missing data were excluded. BR. Missing data were excluded. BS. Missing data were excluded. BT. Missing data were excluded. BU. Missing data were excluded. BV. Missing data were excluded. BV. Missing data were excluded. BW. Missing data were excluded. BX. Missing data were excluded. BY. Missing data were excluded. BZ. Missing data were excluded. CA. Missing data were excluded. CB. Missing data were excluded. CC. Missing data were excluded. CD. Missing data were excluded. CE. Missing data were excluded. CF. Missing data were excluded. CG. Missing data were excluded. CH. Missing data were excluded. CI. Missing data were excluded. CJ. Missing data were excluded. CK. Missing data were excluded. CL. Missing data were excluded. CM. Missing data were excluded. CN. Missing data were excluded. CO. Missing data were excluded. CP. Missing data were excluded. CQ. Missing data were excluded. CR. Missing data were excluded. CS. Missing data were excluded. CT. Missing data were excluded. CU. Missing data were excluded. CV. Missing data were excluded. CV. Missing data were excluded. CW. Missing data were excluded. CX. Missing data were excluded. CY. Missing data were excluded. CZ. Missing data were excluded. DA. Missing data were excluded. DB. Missing data were excluded. DC. Missing data were excluded. DD. Missing data were excluded. DE. Missing data were excluded. DF. Missing data were excluded. DG. Missing data were excluded. DH. Missing data were excluded. DI. Missing data were excluded. DJ. Missing data were excluded. DK. Missing data were excluded. DL. Missing data were excluded. DM. Missing data were excluded. DN. Missing data were excluded. DO. Missing data were excluded. DP. Missing data were excluded. DQ. Missing data were excluded. DR. Missing data were excluded. DS. Missing data were excluded. DT. Missing data were excluded. DU. Missing data were excluded. DV. Missing data were excluded. DV. Missing