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MAJOR ARTICLE

Impact of Tenofovir-Based Pre-exposure Prophylaxis on Biomarkers of Bone Formation, Bone Resorption, and Bone Mineral Metabolism in HIV-Negative Adults

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Background. Pre-exposure prophylaxis (PrEP) with emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) reduces the risk of HIV seroconversion but may promote bone mineral density (BMD) decline. The mechanisms of BMD decline with FTC/TDF remain unclear, and studies in HIV-positive individuals have been confounded by the effects of HIV and concomitant antiretroviral medications. We evaluated the impact of FTC/TDF on biomarkers of bone remodeling and bone mineral metabolism in HIV-negative men and women enrolled in the Partners PrEP Study.

Methods. In a random sample of HIV-negative participants randomized to FTC/TDF PrEP (n = 50) or placebo (n = 50), serum parathyroid hormone (PTH), bone biomarkers (C-telopeptide, procollagen 1 intact N-terminal propeptide, and sclerostin), and plasma fibroblast growth factor 23 were measured at baseline and month 24, and the percentage change was compared between groups. In a complementary analysis, we compared the change in biomarkers between participants with and without a 25% decline in glomerular filtration rate (GFR) on FTC/TDF.

Results. Baseline characteristics were similar between the groups (median age, 38 years; 40% women). Vitamin D insufficiency was common, but baseline GFR and PTH were in the normal range. We observed a significantly greater percent increase in serum C-telopeptide in participants randomized to FTC/TDF vs placebo ($P = .03$), suggesting an increase in bone remodeling. We observed no differences in the other biomarkers, or in a separate analysis comparing participants with and without a decline in GFR.

Conclusions. Increased bone remodeling may mediate the BMD decline observed with tenofovir-containing PrEP and antiretroviral therapy, independent of a TDF-mediated decrease in kidney function.

Keywords. antiretroviral therapy; bone turnover; HIV prevention; kidney; tubular dysfunction.

Daily pre-exposure prophylaxis (PrEP) with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) reduces the risk of HIV seroconversion in individuals at high risk of HIV infection [1, 2]. In HIV-positive individuals, declines in bone mineral density (BMD) after the initiation of antiretroviral therapy are more prominent with the use of TDF-containing regimens [3–6]. Although the mechanism remains unclear, alterations in both kidney and endocrine function have been proposed as contributors to the decline in BMD with TDF-containing antiretroviral therapy (ART). More recently, several studies have demonstrated small but significant declines in BMD with the use of FTC/TDF PrEP in HIV-negative study participants [7–10]. Individuals on PrEP provide a unique opportunity to evaluate mechanisms of BMD decline in the absence of confounding by HIV infection and other ART agents. We sought to characterize the impact of FTC/TDF PrEP on changes in established serum biomarkers of bone formation, bone resorption, and bone mineral metabolism in HIV-negative men and women randomized to FTC/TDF PrEP vs placebo and to evaluate the relationship with markers of kidney injury among participants receiving FTC/TDF. We hypothesized that FTC/TDF PrEP would be associated with increased bone remodeling and that this effect would be independent of TDF-induced changes in kidney function.

METHODS

The Partners PrEP Study was a randomized, placebo-controlled trial of daily oral TDF and co-formulated FTC/TDF to reduce

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the risk of HIV transmission to the HIV-negative partner in serodiscordant heterosexual couples (NCT00557245) [1]. A total of 4758 serodiscordant couples were enrolled in Kenya and Uganda, and HIV-negative partners were randomly assigned to receive daily TDF, FTC/TDF, or placebo for up to 36 months. HIV-negative participants with hepatitis B virus infection, creatinine clearance <60 mL/min, or dipstick proteinuria or glycosuria were excluded. Serum creatinine and electrolytes were measured at baseline and quarterly during the trial, and urine, serum, and plasma samples were archived at –80°C for future analyses. Grade 2 or higher creatinine elevations occurred in <1% of participants and did not differ significantly between the treatment arms. Grade 2 or 3 hypophosphatemia occurred in 9% of participants in each treatment group, and no Grade 4 hypophosphatemia events were reported. Bone fractures were reported in <1% of participants, with no difference between the treatment groups [1].

We previously reported a small but statistically significant decline in estimated glomerular filtration rate (eGFR), as calculated by the Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) equation among participants randomized to active PrEP vs placebo [11]. Although the proportion of participants who experienced a clinically significant decline in eGFR of ≥25% from baseline was higher among participants randomized to active PrEP, this difference did not reach statistical significance. Similarly, in a random sample of participants randomized to FTC/TDF or placebo, we previously described a low incidence of proximal tubulopathy among participants exposed to FTC/TDF (1.7% vs 1.3% in the placebo group; $P = .68$). In that study and for the current analyses, proximal tubulopathy was defined by the presence of at least 2 of the following: tubular proteinuria, euglycemic glycosuria, increased urinary phosphate excretion, and increased urinary uric acid excretion [12].

We conducted 3 separate and complementary analyses. In our primary analysis, the change in bone biomarkers was compared between participants randomized to FTC/TDF vs placebo. In separate analyses, we compared the change in bone biomarkers between participants in the FTC/TDF arm with and without evidence of kidney injury (eGFR decline or hyperphosphaturia), which is a plausible mediator of the effects of TDF on bone. The first analysis included a random sample of participants in the FTC/TDF and placebo arms who had archived serum samples available from baseline and month 24 and paired urine and serum samples available from at least 1 follow-up visit. Participants who became pregnant or who seroconverted before 24 months were excluded from sampling. A separate analysis evaluated the relationship between evidence of kidney injury and changes in bone biomarkers among participants

Table 1. Baseline Characteristics of Participants at Enrollment by Treatment Arm

	FTC/TDF (n = 50)	Placebo (n = 50)
Age, y		
Mean ± SD	38.6 ± 9.3	37.9 ± 9.3
Median (Q1–Q3)	38.5 (31–45)	38 (31–44)
Female gender, No. (%)	20 (40)	20 (40)
No. of children (women only)		
Mean ± SD	3.5 ± 1.3	4.2 ± 2.3
Median (Q1–Q3)	3 (3–4)	4.5 (2–5.5)
Self-reported hormonal contraception use (women only), No. (%)	6 (30)	9 (45)
Body mass index, kg/m^2		
Mean ± SD	22 ± 3.3	22.4 ± 3.1
Median (Q1–Q3)	21.3 (19.9–23.9)	21.6 (20.2–24.5)
Serum creatinine, mg/dL		
Mean ± SD	0.8 ± 0.2	0.8 ± 0.2
Median (Q1–Q3)	0.7 (0.7–0.9)	0.8 (0.7–0.9)
Estimated GFR, mL/min/1.73 m^2		
Mean ± SD	125.0 ± 18.4	124.7 ± 17.4
Median (Q1–Q3)	129.9 (114–139)	124.6 (115–138)
<90 mL/min/1.73 m^2, No. (%)	2 (4)	2 (4)
Serum calcium, mean ± SD, mg/dL	9.1 ± 0.3	9.1 ± 0.4
Serum phosphorus, mean ± SD, mg/dL	3.5 ± 0.6	3.7 ± 0.9
Serum parathyroid hormone, mean ± SD, pg/mL	37.2 ± 14.1	36.6 ± 23.5
Serum 25 hydroxyvitamin D, mean ± SD, ng/mL	25.6 ± 5.9	24.9 ± 7.5
<30 ng/mL, No. (%)	36 (72)	39 (78)
<20 ng/mL, No. (%)	7 (14)	14 (28)
Serum 1, 25 dihydroxyvitamin D, mean ± SD, pg/mL	97.1 ± 32.4	90.2 ± 40.1
Serum 24, 25 dihydroxyvitamin D3, mean ± SD, ng/mL	2.3 ± 0.9	2.4 ± 1.3

All *P* values for comparison between treatment arms were nonsignificant. The *t* test was used for continuous variables, and the chi-square or Fisher exact test was used for categorical variables.

randomized to FTC/TDF PrEP. Participants with an eGFR decline of ≥25% from baseline were frequency-matched by gender and age (within 10 years) in a 1:1 ratio to participants who did not experience a decline in eGFR of ≥25% from baseline and who had no evidence of proximal tubular dysfunction. For descriptive purposes, we also measured bone biomarkers in the 12 participants who were previously identified to have proximal tubulopathy after exposure to FTC/TDF PrEP [12].

Serum intact parathyroid hormone (PTH), C-telopeptide (a biomarker of bone resorption), procollagen 1 intact N-terminal propeptide (P1NP; a biomarker of bone formation), and sclerostin (a WNT inhibitor), and plasma fibroblast growth factor 23 (FGF23; a phosphate regulatory hormone) were measured in archived samples from baseline and month 24. Serum 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D were measured in archived samples from the baseline visit.

The percent change in biomarker levels from study baseline to month 24 was compared between participants in the FTC/TDF and placebo arms and between participants with and without evidence of kidney injury using *t* tests. We estimated that a sample size of 30 participants in each arm would provide 80% power to detect differences in C-telopeptide of the magnitude previously reported in HIV-positive individuals on TDF-containing ART. Because we hypothesized that the differences may be less pronounced in the absence of HIV infection and other ART agents, we planned to include 50 participants from each treatment arm in the primary analysis. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute). All participants provided written informed consent to participate in the Partners PrEP Study, including consent for the use of their archived biospecimens for research related to the safety and efficacy of PrEP. The Partners PrEP protocol was approved by the University of Washington Institutional Review Board and by the ethics review committees at the enrolling sites. The current analysis was also approved by the Institutional Review Board of the Icahn School of Medicine at Mount Sinai.

RESULTS

Baseline characteristics of the study sample were similar between the treatment groups and reflected the demographics of the Partners PrEP Study population (Table 1). Forty percent of participants were women, the majority of whom were multiparous. Use of oral, implantable, or injected hormonal contraceptive methods was reported by 6 women in the FTC/TDF group and 9 women in the placebo group. Baseline levels of serum calcium, phosphorus, PTH, and 25-hydroxyvitamin D were similar between the groups. Baseline 25-hydroxyvitamin D levels were <30 ng/mL in three-quarters of participants and <20 ng/mL in 21% of participants, including a nonsignificant but notably higher proportion of participants in the placebo group.

Table 2. Mean Change in Biomarkers From Baseline to Month 24 Between Treatment Arms

	FTC/TDF (n = 50)				Placebo (n = 50)				
	Baseline	Month 24	Change	% Change	Baseline	Month 24	Change	% Change	*P**
Serum calcium, mg/dL	9.1 ± 0.3	9 ± 0.4	–0.2 ± 0.3	–1.7 ± 3.6	9.1 ± 0.4	8.8 ± 0.3	–0.3 ± 0.4	–2.8 ± 4	0.14
Serum phosphorus, mg/dL	3.5 ± 0.6	3.4 ± 0.6	–0.2 ± 0.7	–2.7 ± 23	3.7 ± 0.9	3.4 ± 1.1	–0.2 ± 1.2	–3.4 ± 30	0.80
Serum PTH, pg/mL	37.2 ± 14.1	37.2 ± 17.2	0.1 ± 18.7	10.3 ± 58.6	36.6 ± 23.5	37.5 ± 14.9	0.8 ± 18.2	16.8 ± 59.8	0.84
Serum sclerostin, ng/mL	0.4 ± 0.1	0.4 ± 0.1	0 ± 0.1	–3.5 ± 20.8	0.4 ± 0.1	0.4 ± 0.2	0 ± 0.1	2.9 ± 20.2	0.24
Serum C-telopeptide, ng/mL	0.4 ± 0.2	0.5 ± 0.3	0.1 ± 0.4	62.7 ± 128.3	0.5 ± 0.6	0.4 ± 0.3	–0.1 ± 0.5	12.3 ± 85.7	0.03
Serum P1NP, µg/L	58.3 ± 25.5	62.5 ± 25.5	3.7 ± 23.6	15.3 ± 47.1	61.6 ± 37.9	55.9 ± 27.1	–4.5 ± 28.5	4.2 ± 39.6	0.13
P1NP/C-telopeptide	186.8 ± 106.5	212.9 ± 198.9	24.4 ± 208.8	39 ± 167.9	173.8 ± 142.5	197.7 ± 163.1	19.4 ± 175.7	36.6 ± 107.3	0.90
Plasma FGF23	86.7 ± 175.1	139.7 ± 309.1	52.9 ± 175.6	56.4 ± 113.2	58.5 ± 62.2	63.9 ± 62.9	5.4 ± 38.1	23.9 ± 55.7	0.07

Abbreviations: FGF23, fibroblast growth factor 23; P1NP, procollagen 1 intact N-terminal propeptide; PTH, intact parathyroid hormone.
* *P* value by *t* test.

Table 3. Baseline Characteristics of Participants Randomized to FTC/TDF With and Without a Clinically Significant Decline in eGFR

	≥25% eGFR Decline (n = 35)	<25% eGFR Decline (n = 35)
Age, y		
Mean ± SD	37.8 ± 7.6	38.8 ± 9.8
Median (Q1–Q3)	39 (32–42)	38 (31–48)
Female gender, No. (%)	18 (51.4)	18 (51.4)
No. of children (women only)		
Mean ± SD	4.2 ± 1.9	3.9 ± 2.6
Median (Q1–Q3)	4.5 (3–6)	3.5 (2–6)
Self-reported hormonal contraceptive use (women only), No. (%)	6 (33.3)	13 (72.2)
Body mass index, kg/m^2		
Mean ± SD	22.6 ± 3.6	21.6 ± 2.2
Median (Q1–Q3)	21.9 (20.5–24.3)	21.4 (20.2–23.3)
Creatinine, mg/dL		
Mean ± SD	0.8 ± 0.1	0.8 ± 0.2
Median (Q1–Q3)	0.7 (0.7–0.9)	0.8 (0.7–0.9)
Estimated GFR, mL/min/1.73 m^2		
Mean ± SD	128.5 ± 13.3	123.9 ± 17.3
Median (Q1–Q3)	129.2 (122–136)	125.6 (117–136)
<90 mL/min/1.73 m^2, No. (%)	0	2 (5.7)
Serum calcium, mean ± SD, mg/dL	9.1 ± 0.4	9 ± 0.4
Serum phosphorus, mean ± SD, mg/dL	3.5 ± 0.7	3.8 ± 0.8
Serum parathyroid hormone, mean ± SD, pg/mL	33.7 ± 14.8	37.7 ± 17.6
Serum 25 hydroxyvitamin D, mean ± SD, ng/mL	25.4 ± 6.3	25.8 ± 6.6
<30 ng/mL, No. (%)	29 (83)	25 (71)
<20 ng/mL, No. (%)	6 (17)	6 (17)
Serum 1, 25 dihydroxyvitamin D, mean ± SD, pg/mL	94 ± 38.8	93.9 ± 23.9
Serum 24, 25 dihydroxyvitamin D3, mean ± SD, ng/mL	2.1 ± 1.1	2.4 ± 1.1

All *P* values for comparison between treatment arms were nonsignificant. The *t* test was used for continuous variables, and the chi-square or Fisher exact test was used for categorical variables.

The absolute and percentage change in bone formation and resorption markers, PTH, FGF23, and sclerostin from baseline to month 24 are summarized in Table 2 for participants randomized to FTC/TDF PrEP vs placebo. The only significant difference between the 2 groups was in serum C-telopeptide, with a greater percent increase observed in participants randomized to FTC/TDF PrEP vs placebo (63% vs 12%, respectively; $P = .03$). There was also a greater percent increase in FGF23 in the active PrEP arm, but this difference did not reach statistical significance (56.4% vs 23.9%, respectively; $P = .07$); the results were similar when extreme outliers with supraphysiologic FGF23 levels at baseline were excluded.

In a complementary analysis among participants randomized to FTC/TDF PrEP, participants who developed a clinically significant ≥25% decline in eGFR were compared with matched participants without evidence of kidney injury. The groups were similar at baseline (Table 3). Although there was a higher rate of self-reported hormonal contraceptive use among women who did not develop evidence of kidney disease, the numbers were small. We observed no significant differences in the percent change in the bone turnover markers PTH, FGF23, and sclerostin between the groups (Table 4). As expected, there was a significantly greater percent increase in serum creatinine in participants who experienced a clinically significant decline in eGFR.

The change in the bone turnover markers PTH, FGF23, and sclerostin in participants who developed proximal tubulopathy during FTC/TDF exposure is summarized in Supplementary Table 1. The only significant change was in PTH, which increased from baseline to month 24 in these participants ($P = .02$).

DISCUSSION

In this secondary analysis of a randomized, placebo-controlled trial, we observed a significantly greater percent increase in the bone resorption marker C-telopeptide in HIV-negative men and women randomized to FTC/TDF PrEP vs placebo. In contrast to prior studies, we did not observe a significant increase in PTH with FTC/TDF exposure [9, 13]. PTH did increase significantly among the small number of participants who developed proximal tubulopathy while on active PrEP, which may reflect the impact of PTH on phosphaturia, one of the characteristics that contributed to the definition of proximal tubulopathy used in our study. Similar to previous studies, we observed no relationship between markers of tenofovir-induced kidney injury and the change in bone biomarkers [9]. These results, in

Table 4. Mean Change in Biomarkers From Baseline to Month 24 Between Participants With and Without ≥25% eGFR Reduction

	≥ 25% eGFR Reduction (n = 35)				<25% eGFR Reduction (n = 35)					
	Baseline	Month 24	Change	% Change	Baseline	Month 24	Change	% Change	T-Statistics	*P**
Sclerostin, ng/mL	0.4 ± 0.1	0.4 ± 0.1	0 ± 0.1	2.6 ± 23.9	0.4 ± 0.1	0.4 ± 0.2	0 ± 0.1	1.4 ± 20.2	–0.2	0.82
Serum C-telopeptide, ng/mL	0.4 ± 0.3	0.5 ± 0.3	0.1 ± 0.4	40 ± 104.4	0.4 ± 0.2	0.5 ± 0.3	0.1 ± 0.3	51 ± 93.2	–0.5	0.61
Serum P1NP, µg/L	71.1 ± 378	90.1 ± 52.9	19.1 ± 35	28.7 ± 52	56.4 ± 25	67.4 ± 31.2	10.4 ± 28.1	27.7 ± 57.1	1.1	0.27
Serum calcium, mg/dL	9.1 ± 0.4	9 ± 0.4	–0.1 ± 0.4	–0.5 ± 4.9	9 ± 0.4	8.9 ± 0.4	–0.1 ± 0.4	–1 ± 4.3	0.4	0.67
Serum creatinine, mg/dL	0.9 ± 0.2	1 ± 0.2	0.1 ± 0.2	11.8 ± 22.4	0.8 ± 0.2	0.8 ± 0.1	0 ± 0.1	1.1 ± 19.9	2.3	0.02
Serum PTH, pg/mL	33.7 ± 14.8	36.4 ± 19.4	2.7 ± 17.7	17.5 ± 65.3	37.7 ± 17.6	37 ± 16.5	–0.7 ± 20.2	12.3 ± 58.4	0.7	0.46
Serum phosphorus, mg/dL	3.5 ± 0.7	3.5 ± 0.7	–0.1 ± 0.9	–0.3 ± 21.1	3.8 ± 0.8	3.5 ± 0.8	–0.3 ± 1.1	–5.5 ± 26.8	1.0	0.32
P1NP/C-telopeptide	226.8 ± 181.2	307.9 ± 316.6	81.2 ± 310.7	66.8 ± 198.8	168.6 ± 97.9	178.3 ± 136	7 ± 170.2	39.3 ± 169.6	1.2	0.23
FGF23	78.7 ± 99.7	121.5 ± 239.2	42.8 ± 170.6	60.1 ± 211.2	72.4 ± 69.5	148.1 ± 458.4	75.7 ± 433.6	58.8 ± 216.5	–0.4	0.68

Abbreviations: FGF23, fibroblast growth factor 23; P1NP, procollagen 1 intact N-terminal propeptide; PTH, intact parathyroid hormone.

* *P* value by *t* test. All participants in this analysis were randomized to active PrEP.

the absence of confounding by HIV infection and other ART agents, suggest that increased bone remodeling, independent of TDF-induced kidney injury, is the primary contributor to BMD decline during TDF exposure. Our results are consistent with a small study of bone biomarkers in HIV-negative men exposed to FTC/TDF PrEP, which also demonstrated a significant increase in serum C-telopeptide levels from baseline [9]. That study also demonstrated a significantly greater increase in levels of the bone formation marker serum osteocalcin in men with higher tenofovir exposure. Although studies in HIV-positive individuals are subject to confounding as a result of HIV infection and other antiretroviral agents, several studies have also reported a similar increase in biomarkers of bone turnover with FTC/TDF use for HIV treatment [14–15]. Taken together, these results support the conclusion that FTC/TDF increases bone remodeling.

The results of our study should be interpreted in light of several limitations. First, the change in bone biomarkers was assessed at a single time point after 24 months of TDF exposure and may not fully reflect the early changes that result in BMD decline. Second, we did not measure plasma drug concentrations in our study sample. Nonetheless, self-reported adherence was >95% in the Partners PrEP Study, and more than 80% of participants in a previous substudy had plasma drug exposure consistent with daily use. Third, we did not perform bone densitometry or bone biopsy in our study. Prior studies have consistently demonstrated significant declines in BMD with the initiation of TDF-based PrEP or antiretroviral therapy, and the goal of the current analysis was to evaluate the potential mechanisms of BMD loss in this setting. Although bone biopsy may provide additional information about TDF effects on bone cell activity and bone mineralization, bone turnover makers are more reflective of global bone remodeling than just activity at the iliac crest. Fourth, our study sample was relatively small and it is possible that we lacked the power to detect small differences between the groups, particularly given the small number of participants with significant eGFR decline. Nonetheless, it is reassuring that we were able detect the small difference in serum creatinine that was expected between participants with and without a clinically significant decline in eGFR. In addition, we observed a significant increase in bone turnover in our population despite the very low incidence of subclinical kidney injury as measured by eGFR decline or evidence of proximal tubular dysfunction, supporting our conclusion that this effect is independent of TDF-induced kidney injury. Fifth, our study included only African participants enrolled in Kenya and Uganda and may not reflect the mechanisms of TDF-induced BMD loss in other patient populations. In addition, we assessed the change in bone biomarkers at a single time point, 24 months after randomization, and it is possible that FTC/TDF may have other effects on bone at earlier time points or with more prolonged exposure. Nonetheless, an increase in bone remodeling

has also been reported in young men of diverse race/ethnicity exposed to FTC/TDF PrEP, suggesting that this is an important contributor to the bone loss observed with TDF exposure [9]. Vitamin D insufficiency was also very common in our population, and it is unknown whether these findings are generalizable to individuals with optimal vitamin D status.

These results provide additional evidence that tenofovir-induced declines in BMD are mediated by an increase in bone remodeling that appears to be independent of kidney injury. These findings may also be relevant to the use of tenofovir alafenamide in patients with advanced chronic kidney disease, who are exposed to similar plasma concentrations of tenofovir as individuals with normal kidney function who are taking TDF [16]. Future studies should evaluate the impact of vitamin D supplementation, which has been shown to reduce bone remodeling in other settings [14, 17] and which may offset some of the adverse effects of tenofovir on BMD in individuals at higher risk of fracture, in younger individuals who have not yet achieved peak bone mass, and in individuals who will be exposed to tenofovir-based PrEP for a prolonged period.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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