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BRIEF REPORT

Changes in Bone Mass After Discontinuation of Preexposure Prophylaxis With Tenofovir Disoproxil Fumarate/Emtricitabine in Young Men Who Have Sex With Men: Extension Phase Results of Adolescent Trials Network Protocols 110 and 113

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Human immunodeficiency virus–seronegative men aged 15–22 years who lost bone mineral density (BMD) during tenofovir disoproxil fumarate/emtricitabine preexposure prophylaxis (PrEP) showed BMD recovery 48 weeks following PrEP discontinuation. Lumbar spine and whole body BMD *z*-scores remained below baseline 48 weeks off PrEP in participants aged 15–19 years.

Clinical Trials Registration. NCT01772823 (ATN 110) and NCT01769456 (ATN 113).

Keywords. preexposure prophylaxis; adolescents; men who have sex with men; bone mineral density; tenofovir disoproxil fumarate.

Preexposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF), alone or with emtricitabine (TDF/FTC), causes modest bone loss in human immunodeficiency virus (HIV)–seronegative adult men who have sex with men (MSM) [1, 2], with the magnitude of loss related to adherence measured by drug exposure [2, 3]. TDF/FTC PrEP use in adolescents and young adult MSM (YMSM) raises concerns because bone growth continues into early adulthood [4]. Peak bone mass, typically achieved when in the mid-20s, predicts bone fractures in later life [5]. Drugs that decrease bone mass or limit bone growth during adolescence might increase fracture risk during adulthood.

In adult MSM, bone loss during TDF/FTC PrEP reverses with TDF/FTC discontinuation [6]. Our aim in this study was to determine whether bone loss reverses with discontinuation of PrEP in YMSM.

METHODS

Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) Protocols 110 (ages 18–22 years) [7] and 113 (ages 15–17 years) [8] were 48-week open-label studies of TDF/FTC PrEP in YMSM with HIV acquisition risk. Study designs were identical. After baseline testing, all participants were offered FTC/TDF (Truvada), 1 tablet by mouth daily for 48 weeks. Specimens to quantify red blood cell tenofovir diphosphate (TFV-DP) concentrations [9] were collected at each follow-up visit to measure adherence. The studies were approved by each participating center's local institutional review boards, and participants' written consent was obtained prior to enrollment.

Exclusions and study procedures have been described elsewhere [7, 8]. Assessments at baseline and each study visit included serum creatinine and other chemistries. At baseline, weeks 24 and 48 bone mineral density (BMD) and bone mineral content (BMC) were measured using dual-energy X-ray absorptiometry (DXA) at lumbar spine (L1–L4; LS-BMD), total hip (HIP-BMD), and whole body BMD (WB-BMD) and whole body BMC (WB-BMC). Machine-generated *z* scores were used.

A preplanned extension phase (EPH) in participants who lost or failed to accrue bone and/or showed evidence of renal toxicity at 48 weeks of PrEP was designed to determine whether toxicity reversed following TDF/FTC discontinuation. Criteria for inclusion in EPH ("EPH-eligible") were 1 or more of the following, present at week 48: for participants aged <20 years, no increase in WB-BMD, WB-BMC, or LS-BMD; for participants aged ≥20 years, ≥1% decrease in WB-BMD or BMD in the total hip, femoral neck, or spine; for all ages, decrease in BMD *z* score of ≥0.5 in total hip, femoral neck, or spine; confirmed ≥ grade 1 serum creatinine, increase in serum creatinine ≥50% from baseline, estimated glomerular filtration rate <60 mL/min/1.73 m^2; or other grade ≥2 nephrotoxicity. Participants who met ≥1 criterion were to immediately enter the EPH when week 48 data were available, after which DXA and laboratory assessments were performed 24 (EPH1) and 48 (EPH2) weeks after discontinuation of study-provided PrEP.

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This analysis pools results from ATN 110 and 113. Continuous variables are presented as the mean ± standard deviation. We compared baseline characteristics between EPH-eligible and non–EPH-eligible participants. In EPH-eligible participants, we compared variables by age groups reflecting biology of bone development and to balance group size: age 15–19 years, with rapid accrual of bone [4], and age 20–22 years, when bone accrual slows. BMD changes were analyzed as percent change for BMD and absolute change for BMD *z* score. *P* values were calculated using independent *t* tests and χ^2 tests for differences in baseline characteristics, paired *t* tests for change between time points, and independent *t* tests for longitudinal changes by age group.

We report change in BMD and BMD *z* score from baseline to week 48 (TDF/FTC effect), week 48 to EPH2 (recovery after stopping TDF/FTC), and baseline to EPH2 (overall change).

RESULTS

Overall, 278 participants were enrolled (Supplementary Figure 1). Bone changes during PrEP have been reported elsewhere [7, 8]. EPH eligibility was assessed in 179 participants who completed the week 48 visit with DXA and 120 (67%) who met ≥1 EPH criterion (119 bone, 1 renal). Twelve EPH-eligible participants discontinued before EPH data were collected. Seventeen continued PrEP through other medical providers (analyzed separately). Ninety-one participants who remained HIV-seronegative with ≥1 EPH visit and no further PrEP use are the basis of this report. There were no differences in age, race/ethnicity, or body mass index among these 91 participants compared to those EPH-eligible participants who discontinued the study or continued PrEP.

Five participants with HIV seroconversion during EPH were excluded after the last seronegative test. The participant who met renal toxicity criteria had a serum creatinine increase >50% from baseline and returned to baseline during EPH, always within the normal range.

Baseline Characteristics of EPH-eligible Participants

Compared to those who did not meet EPH criteria, EPH-eligible participants were older, with higher WB-BMD and WB-BMC. In the EPH-eligible group, the average week 48 TFV-DP concentrations were higher, and a greater proportion of EPH-eligible participants had TFV-DP ≥700 fmol/punch, consistent with ≥4 doses per week on average [10] (Supplementary Table 1).

BMD Changes With Time

LS-BMD, HIP-BMD, and WB-BMD declined by PrEP week 24, rebounded to baseline by PrEP week 48 (LS-BMD and WB-BMD), increased following PrEP discontinuation, and were at (HIP-BMD and WB-BMD) or above (LS-BMD) baseline by EPH2 (Table 1; Supplementary Figure 2A).

The *z* scores for spine, hip, and whole body BMD (LS-BMD-Z, HIP-BMD-Z, WB-BMD-Z) declined by PrEP week 24, remained below baseline throughout PrEP, and were below (LS-BMD-Z and WB-BMD-Z) or at (HIP-BMD-Z) baseline after PrEP was stopped (Table 1, Supplementary Figure 2B).

LS-BMD-Z and WB-BMD-Z declined more during PrEP in participants aged 15–19 years compared to those aged 20–22 years and stayed below baseline after PrEP discontinuation in the younger but not the older age group (Table 1, Supplementary Figure 2C). HIP-BMD-Z had a similar pattern; however, by EPH2, there was no difference in HIP-BMD-Z between age groups (Table 1). LS-BMD and HIP-BMD percent change during PrEP and EPH did not differ significantly by age group (data not shown).

The 17 participants who continued PrEP after the initial 48 weeks of study had progressive decline in LS-BMD-Z and HIP-BMD-Z during EPH, remaining below baseline at EPH2 (Table 1).

DISCUSSION

In this study, we showed that YMSM with bone loss during 48 weeks of PrEP had partial or full BMD improvement during 48 weeks after PrEP discontinuation. However, LS-BMD-Z and WB-BMD-Z stayed below baseline for the duration of follow-up, driven by larger declines in participants aged 15–19 years.

Consideration of *z* scores, which standardize BMD for age, race, and sex, is most important during adolescence when BMD variability increases [4]. *z* scores are stable over at least 3 years during periods of rapid bone accrual [11]. Persistent *z* score decline after stopping PrEP, especially in younger participants, is a concerning finding of this analysis.

We found variability in BMD recovery between hip and spine, with persistent bone loss in spine but not hip after stopping PrEP. Other studies have shown variability in BMD recovery after PrEP. African women who are not living with HIV showed spine and hip BMD improvement by week 48 after stopping PrEP [12]. In adult MSM, spine BMD returned to baseline but hip BMD remained below baseline at 24 weeks off PrEP [6], although participants aged <25 years had rebound in both spine and hip BMD by 48 weeks off PrEP [6]. The younger age of our participants with the most sustained BMD *z* score decline may contribute to observed differences, although exact reasons for the variability remain unclear.

LS-BMD-Z remained below baseline after 48 weeks without PrEP, while HIP-BMD-Z returned to baseline. Low LS-BMD-Z has been noted in high-risk, HIV-seronegative YMSM even without TDF use [1, 13, 14]. Suggested causes for low LS-BMD-Z in this population include vitamin D deficiency/insufficiency [1], amphetamine or inhalant use [1], and being underweight [15].

Table 1. Change in Bone Mineral Density and Bone Mineral Density *z* Score During Different Periods of the Study

PrEP Status during EPH	Variable Measured	Participant Age Category and Number at Week 48	Measurement Site	Change from[a]					
				Baseline to Week 48		Week 48 to EPH2		Baseline to EPH2	
				Value	*P* Value[b]	Value	*P* Value	Value	*P* Value
Off PrEP at week 48	Bone mineral density, g/cm^2: percent change	All participants N = 91	Lumbar spine	−0.001 ± 0.028	.663	0.012 ± 0.034	.002	0.010 ± 0.037	.014
			Hip	−0.014 ± 0.035	<.001	0.010 ± 0.037	.024	−0.003 ± 0.043	.523
			Whole body	−0.005 ± 0.028	.072	0.007 ± 0.024	.008	0.000 ± 0.030	.896
	Bone mineral density *z* score: absolute change	All participants N = 91	**Lumbar spine**	**−0.163 ± 0.274**[c]	**<.001**	**−0.005 ± 0.310**	**.883**	**−0.171 ± 0.358**[c]	**<.001**
			Hip	−0.114 ± 0.294	<.001	0.054 ± 0.273	.101	−0.048 ± 0.312	.092
			Whole body	**−0.135 ± 0.290**[c]	**<.001**	**0.038 ± 0.251**	**.193**	**−0.097 ± 0.297**[c]	**.005**
		Age 15–19 years n = 45	**Lumbar spine**	**−0.258 ± 0.288**[c]	**<.001**	**−0.008 ± 0.270**	**.141**	**−0.261 ± 0.312**[c]	**<.001**
			Hip	−0.150 ± 0.263	<.001	0.056 ± 0.250	.226	−0.074 ± 0.339	.100
			Whole body	**−0.213 ± 0.217**[c]	**<.001**	**0.026 ± 0.247**	**.515**	**−0.174 ± 0.220**[c]	**<.001**
		Age 20–22 years n = 46	Lumbar spine	−0.070 ± 0.227	.043	−0.003 ± 0.348	.964	−0.085 ± 0.382	.174
			Hip	−0.084 ± 0.235	.020	0.053 ± 0.295	.278	−0.026 ± 0.291	.581
			Whole body	−0.059 ± 0.332	.237	0.049 ± 0.258	.246	−0.023 ± 0.344	.677
Continue PrEP after week 48	Bone mineral density *z* score: absolute change	All participants n = 17	**Lumbar spine**	**−0.188 ± 0.229**	**.004**	**0.000 ± 0.222**	**1.000**	**−0.236 ± 0.332**	**.020**
			Hip	**−0.129 ± 0.126**	**.001**	**−0.050 ± 0.207**	**.382**	**−0.186 ± 0.199**	**.004**
			Whole body	−0.065 ± 0.257	.315	−0.100 ± 0.211	.100	−0.150 ± 0.285	.071

Bold typeface identifies rows in which the change from baseline to week 48 and baseline to EPH2 were both statistically significant.

Abbreviations: EPH, extension phase of the study; PrEP, preexposure prophylaxis.

[a]For baseline values, see Supplementary Table 2. Week 48 was when PrEP was discontinued for most study participants. EPH2 was 48 weeks after PrEP discontinuation.

[b]*P* value for the change from beginning to end of each time period by paired t-test.

[c]Difference between age groups $P < .05$ by independent *t* test.

We analyzed an ATN 110/113 participant subset with potential drug toxicity. These results may not apply to all YMSM taking TDF/FTC for PrEP. BMD changes were not compared to a control group but rather with population-standardized norms (z scores), perhaps limiting the precision of our comparisons. The small number of participants aged 15–19 years suggests the need for more studies in that age group.

Participants who were EPH-eligible at week 48 had higher baseline WB-BMD and WB-BMC than those not EPH-eligible. EPH-eligible participants also had higher week 48 drug exposure. Prior reports showed TDF exposure–associated BMD decline in HIV-seronegative MSM [1–3, 7, 8] and women [12]. This suggests that inclusion in this extension phase study is not a statistical effect of reversion to the mean but rather a reflection of drug effect on BMD.

Vitamin D deficiency was associated with bone toxicity in a subgroup of study participants [16]. High vitamin D3 doses (2000 or 4000 IU daily or 50 000 IU monthly) can reverse [17, 18] or mitigate [19] TDF-associated bone loss in persons living with HIV [17, 18] and improve bone turnover markers during PrEP [20]. Further vitamin D supplementation studies during TDF-containing PrEP may be warranted.

The clinical significance of TDF-associated bone loss in YMSM who use PrEP is unclear. In adults living with HIV, some reports show increased TDF-associated fracture rates [21], while others find no association [22]. Higher fracture risk is associated with the concomitant medications cobicistat [23] or lopinavir/ritonavir [21], drugs that are not used in PrEP. A meta-analysis of randomized studies of TDF/FTC PrEP showed no TDF-associated fracture rate increase [24], but follow-up of 4 months to 4 years was too short to provide definitive conclusions.

CONCLUSIONS

LS-BMD-Z and WB-BMD-Z remained below baseline 48 weeks off PrEP in participants aged 15–19 years. While bone toxicity risk is counterbalanced by HIV acquisition protection, there is continued need for strategies to mitigate bone loss in at-risk YMSM during adolescence and early adulthood when bone mass should be accruing.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

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