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Impact of Estimated Pre-Exposure Prophylaxis (PrEP) Adherence Patterns on Bone Mineral Density in a Large PrEP Demonstration Project

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Abstract

Bone mineral density (BMD) declines due to tenofovir-containing pre-exposure prophylaxis (PrEP) have varied among PrEP demonstration projects, potentially related to variable adherence. Characterization of BMD changes in highly adherent individuals, estimated via tenofovir-diphosphate (TFV-DP) levels in dried blood spots (DBS), can assist clinicians when counseling patients. Cisgender men who have sex with men and transwomen in the optional dual-energy X-ray absorptiometry (DXA) substudy of a large, international, open-label PrEP demonstration project, the iPrEx-open-label extension (OLE) study underwent DXA scans and DBS collection every 24 weeks, with average weekly dosing adherence patterns (2, 4, and 7 doses/week) estimated from validated TFV-DP cut-offs. The mean percent BMD change was estimated in strata of average weekly adherence by using a linear mixed-effects model to calculate the BMD decline in highly adherent individuals on PrEP for the first time. DXA/DBS data were available for 254 individuals over a median of 24 weeks in iPrEx-OLE from June 2011 to December 2013. The percent decline in spine BMD was monotonically associated with strata of increasing average weekly adherence ($p < .001$ trend); the p value for trends using hip BMD measurements was .07. Individuals with estimated daily adherence experienced a 1.2% decrease in spine BMD and a 0.5% drop in hip BMD. In highly adherent PrEP users, we found a lower-than-expected drop in BMD when compared with previous studies. This drop is likely not clinically significant for most PrEP users. However, for those at the highest risk of fracture who plan prolonged PrEP use, alternate PrEP strategies could be considered.

Keywords: PrEP, adherence, men who have sex with men, transgender people, bone mineral density, cohort studies

Introduction

Among HIV-infected antiretroviral-naive individuals initiating tenofovir disoproxil fumarate (TDF)-based regimens, declines in bone mineral density (BMD) of up to 5% have been observed in adults, and up to 27% have been seen in pediatric populations.[1–4] The relationship between TDF exposure and fracture risk, however, is less clear.[5–10] Trials of TDF-based pre-exposure prophylaxis (PrEP) have documented smaller decreases in BMD among individuals taking PrEP (up to 2%), and the declines appear to be reversible with discontinuation of TDF.[11–15] Moreover, no PrEP trials have demonstrated an increased fracture risk with the use of TDF/emtricitabine (FTC).[12–18] Guidelines

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have recommended against TDF-containing antiretroviral therapy regimens for those with HIV at risk of bone disease based on potential risk of fracture, although no such recommendation has been made for PrEP based on the current evidence.[19]

TDF-based PrEP studies may be underpowered to detect fracture outcomes given the generally younger, healthier populations enrolled in PrEP trials, leading to the use of BMD as a surrogate.[15,20] Peak bone mass is established in young adulthood and is a strong predictor of fracture risk later in life.[17,21] TDF-based PrEP has been recently approved for adolescents >35 kg.[22] Adolescents and young adults taking PrEP have been observed to have declines, rather than the expected gains in bone mass over time seen in those not on PrEP.[11] Given these concerns, potential bone toxicity has, in part, motivated the testing of alternate PrEP agents and alternative dosing strategies for TDF-based PrEP.[16]

Intermittent PrEP is effective,[23] and it is now recommended by the International AIDS Society-United States guidelines as an alternative for cisgender men who have sex with men (MSM) with infrequent sexual exposures.[19] The motivation for intermittent PrEP has partially been driven by an interest in reducing potential toxicities associated with TDF-containing PrEP regimens.[24,25] However, no study to date has proven that intermittent PrEP decreases the risk of bone or renal-related toxicity.[23] As PrEP uptake expands to include younger and older individuals, and those with more comorbidities than participants enrolled in PrEP clinical trials,[17,26] knowledge of the relationship between PrEP dosing frequency and PrEP-related toxicity is needed. Such information could guide counseling strategies and decision making around daily versus intermittent PrEP, especially for those at higher risk of PrEP-related toxicity who plan on remaining on PrEP for prolonged periods.

Long-term measures of tenofovir (TFV) exposure, such as TFV-diphosphate (TFV-DP) in dried blood spots (DBS) or TFV levels in hair, permit estimation of patterns of cumulative averaged weekly pill-taking over the previous 4 weeks.[27–31] Long-term metrics of PrEP exposure are well suited for evaluating the relationship between cumulative PrEP adherence and toxicities.[29] Protective TFV-DP levels in DBS were associated with greater declines in bone toxicity among adolescents,[32] as were high TFV-DP levels in peripheral blood mononuclear cells in the placebo-controlled iPrEx trial.[15] These studies dichotomized TFV exposure at a single threshold representing ''good'' adherence.[15,32] It is unknown whether BMD decline in highly adherent individuals, such as those who take their medications daily, might differ from previously observed BMD declines among populations with heterogeneous levels of adherence.[13,15,17] Further, although several studies have shown a dose–dependent relationship between TFV-DP levels in DBS and TFV levels in hair with declines in renal function,[30,31] it is unknown whether PrEP-related BMD decline occurs in a dose–dependent fashion.

Materials and Methods

Study design

We analyzed data from an opt-in substudy nested within iPrEx-open-label extension (OLE), an open-label PrEP demonstration project conducted among MSM and transgender women. The bone and metabolic substudy enrolled participants from 7 out of 11 iPrEx-OLE sites in five cities (Cape Town, South Africa; Chiang Mai, Thailand; Lima, Peru; Rio de Janeiro, Brazil; San Francisco, California; and Chicago, Illinois). The study and procedures of both iPrEx-OLE and the bone and metabolic substudy have been previously published.[16,27] The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, the protocol was approved by the institutional review boards at each site, and all participants provided informed consent.

Participants in the bone and metabolic substudy underwent dual-energy X-ray absorptiometry (DXA) to determine BMD at the hip and lumbar spine (L1–L4) at enrollment and every 24 weeks until the end of study participation. The scans were performed with the same protocol at each site. Enrollment in iPrEx-OLE occurred between June 2011 and June 2012, and the last visit for this substudy was in December 2013.

Alcohol use, stimulant use in the past 30 days (any vs. none), and current smoking were assessed at baseline. Excessive alcohol use was considered to be >4 drinks a day based on a threshold of 3 U/day for increased fracture risk,[33] and the categories were defined in the original questionnaire. Body mass index (BMI) was categorized as underweight (<18.5 kg/m^2), normal (18.5–25 kg/m^2), overweight (25–30 kg/m^2), and obese (>30 kg/m^2).

Drug levels

Whole blood was collected for DBS preparation at each visit when DXA scans were performed. We used validated dosing cut-offs for DBS TFV-DP levels to categorize participants into five average weekly adherence categories: daily drug-taking (>1,250 fmol/punch), 4–6 × weekly (700–1,250 fmol/punch), 2–3 × weekly (350–700 fmol/punch), <2 × weekly [below lower limit of quantification (BLQ)-350 fmol/punch], and no drug detected (BLQ).[27,29]

Statistical analysis

An adjusted linear mixed-effects model, using full information maximum likelihood estimation to account for missing data, was used to evaluate predictors of percent (%) decline in BMD at both the spine and hip, including demographics, substance use (excessive alcohol; any stimulant use or smoking), study site, BMI, and average estimated dosing categories. The percent change in BMD over time in each dosing category was estimated by using a linear mixed-effects model.

Results

Characteristics of substudy participants

Of the 1,225 individuals who elected to start PrEP in iPrEx-OLE, 290 enrolled in the DXA substudy. The median time between study end of the original placebo-controlled trial, iPrEx, and OLE enrollment was 79 weeks [interquartile range (IQR): 60 to 89]. During that gap, TDF-based PrEP was not approved in any study country. DBS data and at least one follow-up DXA scan were available for 254 individuals (87%) over a median of 24 weeks. The median age of participants in the DXA substudy was 31 years, and 9% were transgender women; 40% were Latino, 18% were Asian, 15% were Black, and 27% were White (Table 1). The median

Table 1. Sample Characteristics and Predictors of Spine Bone Mineral Density % Change ($N = 254$)

	Overall, %	*Adjusted ß spine BMD % change (95% CI)*	p
Age at study entry, median (IQR)	31 (23–44)	0.02 (–0.03 to 0.06)	.47
Race			
White	27	Ref.	—
Asian	18	–0.56 (–3.59 to 2.47)	.72
Black	15	0.70 (–1.11 to 2.50)	.45
Latino	40	–0.35 (–1.91 to 1.21)	.66
Transgender woman	9	–0.15 (–1.47 to 1.16)	.82
Any stimulant use	5	–0.45 (–2.17 to 1.27)	.61
>4 alcoholic drinks a day	20	–0.40 (–1.33 to 0.52)	.39
Current smoking	35	0.33 (–0.48 to 1.14)	.42
BMI (kg/m^2)			
Low (<18.5)	3	1.77 (–0.46 to 3.99)	.12
Normal (18.5–25)	43	Ref.	—
Overweight (25–30)	43	–0.03 (–0.79 to 0.74)	.95
Obese (>30)	11	–1.24 (–2.48 to 0.10)	.05
Estimated average PrEP pill-taking by DBS			
None	16	Ref.	—
<2 × weekly	26	**−1.06 (−1.70 to −0.42)**	**.001**
2–3 × weekly	13	**−1.38 (−2.32 to −0.44)**	**.004**
4–6 × weekly	21	**−1.14 (−1.97 to −0.31)**	**.007**
Daily	22	**−1.93 (−2.82 to −1.04)**	**<.001**

Bold text: statistically significant at 95% CI level. Individuals in an optional substudy of the iPrEx-open-label extension underwent dual-energy X-ray absorptiometry scans and DBS collection every 24 weeks, with average weekly dosing adherence patterns (2, 4, and 7 doses/week) estimated from validated tenofovir-diphosphate cut-offs. The impact of covariates on BMD change was estimated by using adjusted mixed-effects linear regression. The model was also adjusted for site.

BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DBS, dried blood spot; IQR, interquartile range; PrEP, pre-exposure prophylaxis.

z-score was –0.7 at the spine (IQR: –1.4 to 0.3) and 0.2 at the hip (IQR: –0.7 to 0.4). At baseline, 9% had z-scores less than –2.0 at either spine (median: –2.5, IQR: –2.6 to –2.2) or hip (median: –2.2, IQR: –2.3 to –2.1).[34]

Predictors of % BMD decline

After starting PrEP, 3% developed low z-scores as defined by a z-score falling below –2.0, not including the 9% who had z-scores less than –2.0 at baseline. No fractures occurred among substudy participants during the study. All who newly developed low z-scores had quantifiable TFV-DP levels in DBS, and most (57%) had estimated levels of drug-taking consistent with ≥4 doses a week (≥700 fmol/punch).[27] Overall, BMD decline did not occur after 24 weeks of DXA assessment [–0.33%, 95% confidence interval (CI): –0.67 to 0.00; $p = .05$ at week 24; –0.05%, 95% CI: –0.39 to 0.30; $p = .79$ at week 48; –0.05%, 95% CI: –0.40 to 0.30; $p = .76$ at week 72]. There was a dose–dependent % decline in spine BMD by strata of increasing estimated average weekly adherence over the course of the study ($p < .001$ trend) (Table 1). There was also no difference in the % BMD decline in the subset who had low baseline z-scores versus those who had normal baseline z-scores ($p = .75$). For the hip BMD outcome, a statistically significant dose–dependent % decline occurred at week 24 ($p = .02$ trend), although the p value for trend using hip BMD measurements was .07 by the study end.

In adjusted analysis, only increasing strata of estimated average weekly PrEP adherence ($p < .001$ trend) were associated with spine BMD decline by the study end (Table 1). The association did not differ when stratifying transgender women versus MSM ($p = .57$). For the hip BMD outcome, only high adherence (4–6 doses weekly) versus no detectable drug (ß –0.63, 95% CI: –1.25 to –0.01; $p = .05$) was associated with a statistically significant BMD decline.

Mean % BMD decline by average PrEP adherence

The average mean decline in spine BMD was –1.15% (95% CI: –1.65 to –0.64) among those with estimated daily adherence by TFV-DP DBS level versus –0.53% (95% CI: –1.06 to 0.00) for 4–6 doses per week versus –0.46% (95% CI: –1.31 to 0.39) for 2–3 doses per week versus –0.26% (95% CI: –0.81 to 0.29) for individuals taking <2 doses per week (Fig. 1). There was a 0.72% increase (95% CI: 0.20 to 1.25) in spine BMD among those who were not taking PrEP (TFV-DP BLQ). At the hip, the mean decline in BMD was –0.50% (95% CI: –0.94 to 0.07) for those with estimated daily adherence versus –0.75% (95% CI: –1.16 to –0.32) for 4–6 doses per week versus –0.70% (95% CI: –1.26 to –0.14) for 2–3 doses per week versus –0.43% (95% CI: –0.83 to –0.02) for <2 doses per week, compared with –0.03% (95% CI: –0.45 to 0.39) among those who were not taking PrEP.

Discussion

In the iPrEx-OLE demonstration project, we found a monotonic decrease in BMD with higher weekly PrEP adherence as estimated by an objective long-term metric of TFV exposure. However, we observed only approximately a 1% drop in spine BMD and a half percent decrease in hip BMD among PrEP users with very high adherence over a median of 24 weeks. Even when using a DBS drug-level cut-off consistent with estimated daily/very high adherence, the

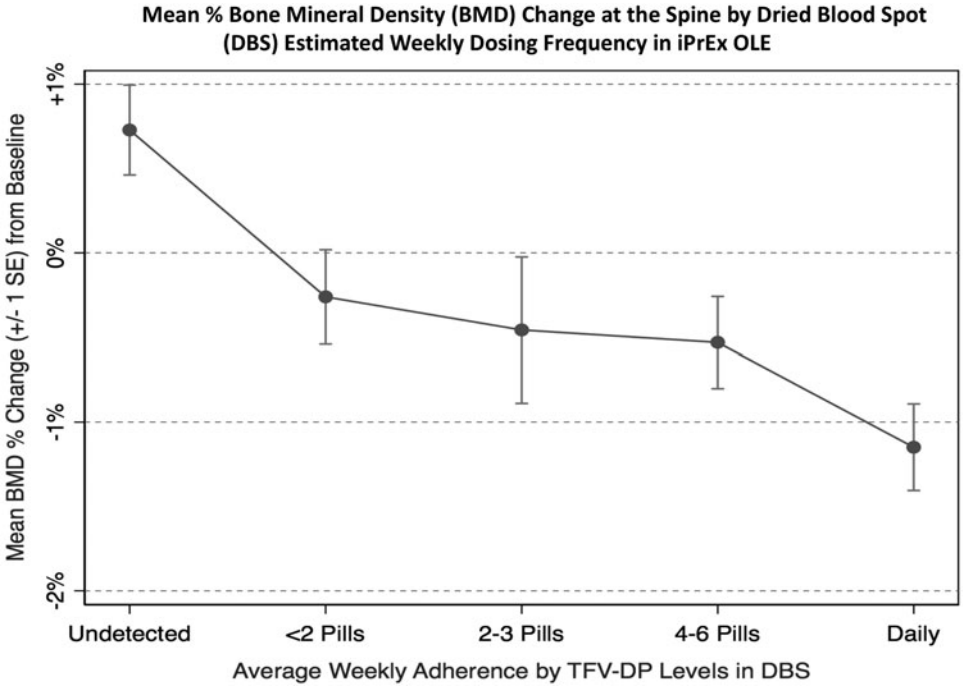

FIG. 1. The average mean change in bone mineral density at the spine over the study period (median 24 weeks) is plotted within strata of estimated average weekly preexposure prophylaxis dosing frequency based on validated dosing cut-offs from TFV-DP levels in DBS. BMD, bone mineral density; DBS, dried blood spot; OLE, open-label extension; SE, standard error; TFV-DP, tenofovir-diphosphate.

decline was reassuringly similar or lower than that observed in most prior PrEP studies.[11,13–15] By employing a long-term metric of exposure stratified into multiple dosing categories, we were also able to define the average and dose–dependent decline in spine BMD with daily (−1.15%) versus less frequent estimated adherence patterns (less than −0.53% for <4 doses weekly).

In this relatively young, healthy study population, almost a tenth of the sample had low *z*-scores at baseline and 3% developed a low *z*-score over the course of <6 months on PrEP. This higher-than-expected proportion of MSM and transgender women with low *z*-scores at baseline is similar to what has been observed in other studies of healthy, younger participants at risk for HIV, with the mechanism and clinical implications currently unclear, although one study found an association with stimulant use.[14,15] The association between TDF-containing PrEP and BMD decline and/or fracture should be examined in studies with longer follow-up time and/or in populations at higher risk of fracture, such as older adults initiating PrEP, to better define PrEP's risks on bone health among diverse populations at risk of HIV.[26]

We found a monotonic dose–response relationship between TDF/FTC pill-taking and toxicity. For those planning prolonged daily PrEP use who are at high risk of fracture, alternate PrEP strategies such as TFV alafenamide-based PrEP could be considered once available.[35] Dose-limiting strategies such as intermittent TDF/FTC-based PrEP could also potentially reduce risks of bone toxicity if that strategy were preferred by the PrEP user, although additional research is needed comparing toxicity in daily versus intermittent use. However, given the modest declines seen with even very high adherence in our study, these differences are likely clinically significant only for those at the highest risk of bone toxicity. Obtaining baseline DXA scans in all PrEP initiators is likely not cost-effective, and our data suggest that a low *z*-score at baseline does not modify the effect of TDF on subsequent BMD decline. Instead, individuals at high risk of fracture based on other risk factors and comorbidities, such as stimulant use, glucocorticoid use, etc.,[14,34] should be monitored closely. Alternative PrEP agents, once available, could also be considered in those at risk of bone or renal toxicity. Future studies would preferably include objective metrics of long-term exposure to TDF to assess the relationship between cumulative drug exposure and BMD decline, including in populations using intermittent PrEP. Inclusion of long-term metrics of drug exposure with validated dosing cut-offs can, to a degree, overcome the impact of variable adherence when interpreting the risks and benefits of medications in PrEP trials and roll-out projects.[27]

Limitations of the DXA substudy include the opt-in nature of the cohort. For instance, individuals electing to receive DXA scans could exhibit greater health-seeking behaviors on average, which could lead to underestimation of the intervention's risks, and/or impact generalizability. It is unknown whether prior receipt of TDF-based PrEP could have impacted BMD declines (median 79 weeks off PrEP); however, a prior analysis suggested that BMD in TDF/FTC PrEP users returned to baseline on average 48 weeks after discontinuation of the medication.[16] Given that transgender women were <10% of the sample, estimates are less precise for transgender women. Finally, given the short follow-up time and the younger, healthy MSM and transgender women population studied in iPrEx-OLE, this study was not designed to explore the risk of fracture or BMD decline in the long term.

TDF/FTC PrEP users with daily/very high adherence experienced only ∼a 1% average decline in BMD in the spine and a 0.5% decrease in the hip, lower than expected based on prior studies. Given the monotonic relationship between PrEP pill-taking behavior and TDF-related bone toxicity, individuals at the highest risk for fracture could consider alternate PrEP strategies if they plan to use PrEP for prolonged periods.

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