

Title: Recovery of Bone Mineral Density Following Discontinuation of Tenofovir-Based HIV Pre-Exposure Prophylaxis

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Running Title: Bone Recovery After PrEP discontinuation

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ABSTRACT

Background: Oral tenofovir disoproxil fumarate (TDF) for HIV prevention and treatment is associated with decreases in bone mineral density (BMD). Previous reports suggest that these changes may be reversible after discontinuation of TDF.

Setting: A metabolic substudy of 498 participants in a randomized, placebo-controlled HIV prevention trial of oral co-formulated TDF with emtricitabine (TDF/FTC, Truvada®) for HIV preexposure prophylaxis (PrEP) enrolling a global sample of men who have sex with men and trans women.

Methods: Participants underwent dual X-ray absorptiometry (DXA) to quantify bone mineral density (BMD) in the hip and spine during PrEP and at 2 visits after stopping (median of 23 and 79 weeks post-PrEP, respectively). Results are stratified by pharmacologic measure of TDF/FTC adherence.

Results: There was no significant difference in change in hip/spine BMD at any timepoint between placebo and those with low adherence. Adherent participants had a mean (standard error) BMD change at TDF/FTC discontinuation of -1.02% (0.24) in the hip and -1.84% (0.36) in the spine. After stop, annualized BMD increases of 1.13% per year (0.27) in hip and 1.81% per year (0.36) in spine BMD were observed in adherent participants compared with 0.19% (0.16) and 0.74% (0.21) in the placebo group, respectively ($p=0.003$, both comparisons). On average, BMD returned to baseline levels by 1 year after PrEP stop. Recovery was consistent across age, baseline BMD z-score and treatment duration.

Conclusions: Mean BMD returns to baseline levels within 12-18 months after TDF-based PrEP discontinuation in both hip and spine with consistency across participant subgroups.

Keywords: Pre-exposure Prophylaxis; tenofovir/emtricitabine; PrEP; bone mineral density; DXA scan

INTRODUCTION

Randomized trials have demonstrated that pre-exposure prophylaxis (PrEP) with oral tenofovir disoproxil fumarate (TDF) or co-formulated TDF with emtricitabine (TDF/FTC, Truvada®) prevents human immunodeficiency virus (HIV) acquisition (1-6). In HIV treatment, TDF-based therapy has been associated with decreases in bone mineral density (BMD) with unclear clinical significance (7); some studies have found that TDF is associated with increased fracture risk while others have not (8-12). HIV therapy switch studies have found that substitution of TDF leads to some BMD recovery, suggesting BMD changes are reversible (13-15).

Trials of TDF-based PrEP have documented BMD decreases of 0.5 to 1.5% with no clear excess fracture signal (16-19). Bone toxicity has partially motivated the testing of alternative PrEP agents. Recently the MTN 003B PrEP trial (19), found reversible BMD changes after withdrawal of TDF-PrEP in a cohort of young African women. We examine the trajectory of BMD changes through extended follow-up of the iPrEx studies (1, 20).

METHODS

Study design: We analyzed an opt-in substudy nested in a placebo-controlled randomized clinical trial (iPrEx study) of daily oral TDF/FTC for PrEP in men who have sex with men and transgender women (MSM/TW). The bone and metabolic substudy enrolled at 7 of 11 iPrEx sites – in 5 cities (Cape Town, South Africa; Chiang Mai, Thailand; Lima, Peru; Rio de Janeiro, Brazil; San Francisco, USA) with a target enrollment of 500 and achieved enrollment of 498 HIV-uninfected volunteers. The study conduct

was consistent with the Declaration of Helsinki; the protocol was approved by the ethics committee at each site and all participants provided written informed consent.

Participants underwent dual X-ray absorptiometry (DXA) to quantify bone mineral density (BMD) in the hip and spine at enrollment and every 24 weeks until study drug stop (stop visit) and 24 weeks after discontinuation of study drug (post-stop visit). The scans using the same protocol across sites. The full methods and results for iPrEx have been published previously (1,20) and for the bone substudy (16). After a gap in participation, volunteers were invited to enroll in the iPrEx open label extension (OLE), which offered TDF/FTC for up to 18 months. The population and procedures for iPrEx OLE have been reported previously (20). DXA participants from iPrEx were scanned at entry into iPrEx OLE. Randomized study drug was ended for iPrEx participants in August 2010 and enrollment in iPrEx OLE occurred between June 2011 and June 2012.

Drug Levels: All DXA participants randomized to TDF/FTC underwent drug level testing for tenofovir and its metabolites in samples collected during the clinical trial (21). Of particular interest are levels of tenofovir diphosphate (TFV-DP) in viably cryopreserved peripheral blood mononuclear cells (vPBMCs) collected at the week 24 visit; these levels showed a linear association with peak loss of BMD in TDF/FTC participants (16). We dichotomized these levels as TFV-DP < 16 v. TFV-DP \geq 16 fmol per million vPBMCs, a level which is associated with a 90% reduction in HIV incidence (21) and use of approximately 2-3 tablets per week on average (21).

Statistical Analysis: We examined BMD levels at 5 time points: iPrEx enrollment, iPrEx week 24, the iPrEx stop visit, 24 weeks post-stop, and at OLE enrollment. We compared BMD for those on placebo versus TDF/FTC randomization and then further by the week 24 TFV-DP levels in PBMCs (TFV-DP < 16 v. TFV-DP \geq 16).

Average percentage BMD changes from baseline in hip and spine were compared across groups (TDF/FTC v. placebo and TFV-DP < 16, TFV-DP ≥ 16 v. placebo) by a linear mixed effects model with an unstructured covariance matrix (22). We examined consistency of this effect across age, baseline BMD Z-score, gender identity and duration on randomized drug.

The annual rate of BMD change (relative to baseline BMD) after the stop visit comparing TDF/FTC v. placebo and TFV-DP < 16, TFV-DP ≥ 16 v. placebo used a mixed effects model with random slopes and intercepts (22) and allowing for interactions of slope and intercept with randomization/drug exposure in the fixed model.

To address missing DXA scans (29% missed a post-stop and 42% have no OLE DXA), 200 multiple imputations (23) of the BMD values based on values at baseline, week 24, and the stop visit as well as age, race, site, height, weight, lean body mass, and date of stop scan were analyzed with the “mi” package in Stata. Demographics of those with complete and missing DXA scans were compared by the t-test for continuous variables and Fisher exact test for categorical variables. All analyses were performed in Stata 14.

RESULTS

Available Scans Baseline Characteristics: iPrEx enrolled participants from July 2007 through December 2009 with protocol-mandated study drug withdrawal in August 2010 and 24-week post stop scans completed by February 2011. Enrollment in iPrEx OLE opened in June 2011 and closed in July 2012. During that gap, oral TDF/FTC for PrEP was not approved for use in any country. The median (interquartile range, IQR) for enrollment to stop visit was 64 weeks (44-88), from stop to 24-week post-stop was 23 weeks (22-25) and from stop to OLE-enrollment was 79 weeks (60-89).

Of the 498 participants, 24-week post stop scans were available in 352 (71%), and at OLE enrollment

in 289 (58%). All participants have a stop-scan which was post-baseline in 493 (99%) at a median of 64 weeks on study (IQR: 41 to 87).

Baseline characteristics (at iPrEx enrollment) varied slightly across availability of BMD scans at the 24-week post stop visit and OLE enrollment (supplementary Table 1). Older participants were statistically significantly more likely to be scanned after drug stop ($p < 0.001$, 24-week post-stop; $p = 0.01$, OLE entry); however, median age of participants with scans at 24-week post stop (median: 25, IQR: 21 to 34) and OLE enrollment (median: 26 IQR: 21 to 34) was similar to the overall DXA population (median: 25, IQR: 21 to 33). Weeks on study medication was also higher in those with post-stop and OLE entry scan ($p < 0.001$ both comparisons) reflecting those who discontinued study early were less likely to return for post-drug visits or enroll in OLE. The proportion with post-stop and OLE scans varied by enrolling site ranging from 40% to 76% ($p=0.05$) and 26% to 67% ($p < 0.001$), but there was no difference by randomized arm. Among TDF/FTC participants with TFV-DP < 16 fmol, 76% had 24-week scans compared with 80% of those with TFV-DP ≥ 16 ($p = 0.48$). At OLE entry, it was 55% v. 69% ($p=0.04$) with scans, respectively. Overall, older participants, more adherent participants, and those who remained on study drug longer were more likely to be retained for scans after study drug discontinuation.

Post-Stop Changes in BMD:

Figure 1(a) and Figure 2(a) summarize the mean (standard error) percentage change in BMD (hip and spine, respectively) from baseline to week 24, the stop visit, the 24-week post stop visit and OLE entry by placebo and TDF/FTC arms. The TDF/FTC arm is stratified by level of TFV-DP at week 24 to reflect their adherence to TDF/FTC. There is no significant difference in BMD in hip or spine at any timepoint between placebo and TDF/FTC with TFV-DP < 16 fmol/ 10^6 vPBMC. However, those with TFV-DP ≥ 16 fmol have significant decreases in both hip and spine at week 24 and the stop visit: mean (SE) of

-0.85% (0.19) and -1.02% (0.24) in the hip and -1.40% (0.30) and -1.84% (0.36) in the spine. After study drug discontinuation, we observed a BMD increase of 1.13% (0.27) per year among these participants in the hip and 1.81% (0.36) in the spine compared with 0.19% (0.16) in the hip and 0.74% (0.21) in the spine in the placebo group, $p=0.003$ for both comparisons. At OLE entry, mean (SE) BMD in hip and spine was at or above values of the baseline scan with mean (SE) of 0.45% (0.42) and 0.37% (0.52) change (compared to baseline scan) in those with TFV-DP ≥ 16 compared to 0.55% (0.25) and 1.11% (0.32) in placebo participants, $p=0.84$ and $p=0.22$, respectively.

Sensitivity Analyses:

To examine the effect of attrition, multiple imputation was used to infer missing scans based on baseline, week 24, and stop as well as age, race, site, height, weight, lean body mass, and date of stop scan. The results were substantially similar and appear in Figures 1(b) and 2(b) for hip and spine, respectively.

We examined consistency of BMD effects during and after PrEP by comparing subgroups by age (< 25 year at enrollment v. ≥ 25 years at enrollment, Figure 1 and 2 panels (c) and (d), respectively), baseline BMD Z-score (Z-score < -1 at enrollment v. Z-score ≥ 1 , panels (e) and (f), respectively), and duration of randomized study treatment in iPrEx (< 1 year of study treatment v. ≥ 1 year, panels (g) and (h), respectively). The graphs suggest consistent evidence across subgroups of bone loss on study with clear trajectory for recovery at or above baseline levels. Of note, participants ≥ 25 years of age with TFV-DP ≥ 16 at week 24 have BMD in spine (shown in Fig. 2(d)) 0.67% below baseline at OLE entry (95% CI: -1.94% to +0.60%); however, the change is not significantly different from placebo ($p=0.10$). There is no significant association between TDF/FTC duration and recovery in hip or spine BMD. Recovery did vary by site but our sites are heterogeneous in adherence, participant demographics and scan completion, complicating interpretation.

For the 7 transwoman identified participants with TFV-DP ≥ 16 , changes were +0.68% (95% CI: -1.00% to +2.37%) at the stop scan and +3.33% (95% CI: +0.98% to +5.68%) at OLE entry in the hip and -1.35% (-95% CI: -3.19% to +0.49%) at the stop scan and 3.14% (95% CI: -0.64% to +6.92%) at OLE entry in the spine. We saw no evidence of an interaction between treatment and gender identity of BMD recovery ($p=0.86$). There was also consistent evidence of recovery stratifying the active arm using 25 fmol/ 10^6 vPBMC (consistent with at least 4 pills per week of TDF/FTC) at week 24.

DISCUSSION

We reported extended off-drug BMD follow-up in a geographically and demographically diverse sample of MSM/TW. We document increases in BMD after drug discontinuation in TDF/FTC-adherent participants of approximately 1.0% per year relative to placebo (Hip: Placebo, 0.19% per year v. TDF-DP ≥ 16 , 1.13% per year; Spine: Placebo, 0.74% per year v. TDF-DP ≥ 16 , 1.81 per /year). This is consistent with the observation in MTN003B that TDF-PrEP adherent young African women also experienced return to baseline BMD over the year after PrEP discontinuation (19). Both studies suggest full recovery is not evident by 24-weeks post-discontinuation but is evident after stopping oral FTC/TDF PrEP for 48 to 79 weeks.

BMD recovery appears consistent across age, duration of PrEP and baseline BMD. However, our numbers are modest overall and our power is limited to examine recovery in key PrEP populations including those who have not reached peak bone mass, those over 50, people who cycle on/off PrEP, “on demand” users or who use it for periods longer than our cohort. Our numbers are particularly small for TW participants (~7 trans women in the active arm of the substudy with evidence of high adherence); we previously reported that trans women tended to have less BMD decreases during PrEP (24) possibly due to the bone protective effects of feminizing hormones or lower adherence..

We used multiple imputation to account for missing scans. This approach is valid even with a large proportion of missing data. Its validity requires the missing at random assumption (23) that differences in missing and non-missing scan can be explained by variables used for constructing imputations. This assumption can never be fully verified.

A reviewer asked us to assess recovery of phosphorous and estimated glomerular filtration rate. The former was not reduced and hence not recovered. We previously documented the recovery of eGFR after stopping TDF/FTC (25).

This study suggests that discontinuation of TDF/FTC for PrEP will lead to BMD recovery to levels expected in the absence of PrEP in populations of MSM/TW.

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Figure Legends:

Figure 1

Title: Percentage Change in Total Hip Bone Mineral Density (BMD) from Baseline Value by Randomized Treatment and Stratified by Level of Intracellular Tenofovir Diphosphate (TFV-DP) in fmol per Million Viable Cells at Week 24 of Randomized Trial. Bars Indicate One Standard Error.

X-axis (Panels a-h): Time Since iPrEx Randomization

Y-axis (Panels a-h): Percent Change in Total Hip BMD

Panel Headings

- (a) All Participants – Available Scans
- (b) All Participants – Results of Multiple Imputation
- (c) Participants Aged < 25 years at iPrEx Entry
- (d) Participants Aged \geq 25 years at iPrEx Entry
- (e) Baseline Hip Z-score < -1 at iPrEx Entry
- (f) Baseline Hip Z-score \geq 1 at iPrEx Entry
- (g) Duration Randomized Treatment \geq 1 Year
- (h) Duration Randomized Treatment < 1 Year

Footnote:

Black Line: Randomized to Placebo

Red Line: Randomized to TDF/FTC with TFV-DP ≥ 16 at week 24

Blue Line: Randomized TDF/FTC with TFV-DP < 16 at week 24

Figure 2

Title: Percentage Change in L1-L4 Spine Bone Mineral Density (BMD) from Baseline Value by Randomized Treatment and Stratified by Level of Intracellular Tenofovir Diphosphate (TFV-DP) in fmol per Million Viable Cells at Week 24 of Randomized Trial. Bars Indicate One Standard Error.

X-axis (Panels a-h): Time Since iPrEx Randomization

Y-axis (Panels a-h): Percent Change in L1-L4 Spine BMD

Panel Headings

- (a) All Participants – Available Scans
- (b) All Participants – Results of Multiple Imputation
- (c) Participants Aged < 25 years at iPrEx Entry
- (d) Participants Aged ≥ 25 years at iPrEx Entry
- (e) Baseline Spine Z-score < -1 at iPrEx Entry
- (f) Baseline Spine Z-score ≥ 1 at iPrEx Entry
- (g) Duration Randomized Treatment ≥ 1 Year
- (h) Duration Randomized Treatment < 1 Year

Footnote:

Black Line: Randomized to Placebo

Red Line: Randomized to TDF/FTC with TFV-DP ≥ 16 at week 24

Blue Line: Randomized TDF/FTC with TFV-DP < 16 at week 24

ACCEPTED



