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Tenofovir Disoproxil Fumarate/Emtricitabine Prophylaxis Has No Effect on Bone Mineral Density and Bone Mineral Content in African Breastfeeding Women Receiving Pre-Exposure Prophylaxis for HIV

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Background: Tenofovir disoproxil fumarate (TDF) when used as pre-exposure prophylaxis (PrEP) during pregnancy is considered safe overall, however, there is insufficient evidence of its effect on maternal bone. We compared bone mineral density (BMD) and bone mineral content (BMC) at the lumbar spine (LS) and hip of African breastfeeding women exposed and not exposed to TDF-containing PrEP in a randomized control trial (RCT).

Methods: This is a secondary data analysis of an RCT where pregnant women were randomized to initiating PrEP during pregnancy or delayed initiation of PrEP until breastfeeding cessation. BMD and BMC at the LS and hip were measured using dual-energy x-ray absorptiometry (DXA) at 6, 26, 50, and 74 weeks postpartum. In an exploratory analysis, BMD at the hip and LS were evaluated against varying tenofovir levels during pregnancy.

Results: Of 300 women in the RCT who had a DXA at 6 weeks postpartum, 102 (66%) women in the Immediate PrEP arm and 105 (72%) in the Delayed PrEP arm had a 74-week DXA scan. Adjusting for breastfeeding duration and body mass index, there were no significant differences in BMD or BMC at the hip and LS between treatment arms. There was no consistent dose–effect of tenofovir diphosphate detected during pregnancy on BMD at the hip (P = 0.231) or the LS (P = 0.277).

Conclusions: After adjusting for breastfeeding and body mass index, tenofovir disoproxil fumarate when given as oral PrEP during pregnancy had no deleterious effect on BMD and BMC at the hip and LS of African breastfeeding women.

Key Words: tenofovir disoproxil fumarate, pre-exposure prophylaxis, bone mineral content, bone mineral density

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INTRODUCTION

Tenofovir disoproxil fumarate (TDF) has been widely used since 2013 in combination antiretroviral treatment (ART) regimens for pregnant and nonpregnant people living with HIV.[1] However, more recently in nonpregnant adults, TDF is gradually being replaced with tenofovir alafenamide (TAF) or other class-specific antiretroviral drugs after clinical trials that demonstrated noninferior efficacy but better safety outcomes than TDF.[2–4] TDF has been associated with nephrotoxicity and reduced bone mineral density (BMD) in people living with HIV[5–7] and is thought to have a direct effect on bone with resultant increased bone resorption through altered gene expression of both osteoclast activity and osteoblast activity.[8] Other factors such as HIV, contraception, pregnancy, and lactation could also contribute to a decline in BMD.[9] Pregnancy and lactation, in particular, are independently associated with a decline in BMD because of increased calcium metabolism.[10,11] In the PROMISE substudy (IMPAACT P1084s), a significant decline in BMD up to 74 weeks postpartum was observed in breastfeeding

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G.K. and D.M. conceptualized the study, provided oversight of the formal analysis of study data and wrote the first draft of the manuscript. C.L. conducted the formal analysis of study data. J.F.R., R.C., and G.G. provided financial support and resources for the project and assisted with design of the research. Z.G. and A.C.D. played a key role in the conduct of the research and data collection. All authors reviewed, commented on, and approved this manuscript before submission for publication.

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Anonymized participant data will be made available on request directed to the corresponding author.

Clinical Trial Number: CAP016 is on ClinicalTrials.gov, with tracking number NCT3227731 (https://clinicaltrials.gov/ct2/show/NCT03227731).

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women living with HIV receiving TDF-based ART in comparison with women not receiving ART after adjusting for breastfeeding.[12]

TDF is also widely used in combination with emtricitabine (FTC) as pre-exposure prophylaxis (PrEP) in pregnant and nonpregnant people at high risk of contracting HIV, and several PrEP studies have also reported small but significant decreases in BMD in nonpregnant populations receiving TDF-PrEP.[13–15] Only 1 study has examined the effect of TDF used as PrEP on the bones of breastfeeding African women.[16] The purpose of this secondary data analysis of a PrEP during pregnancy randomized control clinical trial is to compare the BMD and bone mineral content (BMC) at the lumbar spine (LS) and hip of breastfeeding African women who were randomized to either initiating PrEP during pregnancy or delayed initiation of PrEP until breastfeeding cessation.[17]

METHODS

Study Design and Participants

The CAP016 open-label randomized controlled clinical trial was designed to examine the safety of TDF/FTC PrEP use during pregnancy and breastfeeding, the primary analysis for which was recently published and is described in detail in the publication.[17] In brief, pregnant women not living with HIV, 18 years or older, at substantial risk for HIV infection, with no serious illnesses, with creatinine clearance of >70 mL/min, <28 weeks gestation, and provided informed consent were randomized to either initiating daily oral TDF/FTC PrEP at enrollment (Immediate PrEP) or delayed TDF/FTC PrEP until breastfeeding cessation (Deferred PrEP). Participants were followed up at monthly intervals during pregnancy and at 3-monthly intervals postdelivery until 18 months.

Demographic information (age, weight, height, parity, household income, and employment status) was collected at baseline during pregnancy. Body mass index (BMI) was calculated (weight [kg]/height^2 [m]) and graded according to World Health Organization categories: underweight (<18, 5), normal (18.5–24.9), overweight (25–29.9), obese (30–34.9), severe obese (>35). Infant feeding practice (breastfeeding or formula feeding and duration) was gathered from participants at 6 weeks then at 3-monthly intervals during their postdelivery visits. Contraception use during the postpartum period was documented at all follow-up visits.

Imaging and Laboratory Assessments

BMD and BMC of the LS and hip of women were measured using dual-energy x-ray absorptiometry (DXA) at 6 weeks, 6, 12, and 18 months postpartum. Participants had DXA scans of the hip and LS performed by a trained radiographer, and BMD (g/cm^2) and BMC (g) at the LS and hip were documented at each visit. These measurements were documented in real time in clinical templates and subsequently transcribed to case report forms for data capturing. Breastfeeding practice was documented at 6 weeks, 6, 12, and 18 months postpartum. The mean BMD and BMC at the LS and hip were compared between the Immediate and Deferred PrEP arms at each visit. In addition, the mean percentage change between 6 and 74 weeks was compared between the Immediate and Deferred PrEP arms.

As a post hoc investigation, tenofovir diphosphate (TFV-DP) concentrations were measured using stored dried blood spots (DBSs) that were collected at 2 visits during pregnancy. Extractions from a 50-μL DBS were tested for TFV-DP using a validated high-performance liquid chromatography–tandem mass spectrometry method at the University of Cape Town, South Africa. The lower limit for TFV-DP quantification was 16.6 fmol/3-mm punch. We extrapolated adherence thresholds against TFV-DP concentrations previously reported in a directly observed daily PrEP study in African pregnant women.[18] In our exploratory analysis, we determined the predictive margins of the mean BMD at the hip and LS for the following TFV-DP concentrations, <200 fmol/punch (equivalent to <2 doses/week), 200–400 fmol/punch (2–4 doses/week), 400–600 fmol/punch (4–6 doses/week), and >600 fmol/punch (7 doses/week).

Data Analysis

For comparisons between Immediate PrEP and Deferred PrEP arms, *t*-tests for numeric data and χ^2 test or Fisher exact test (small frequencies) for categorical data were used. Baseline comparisons applied Wilcoxon/Kruskal–Wallis tests for continuous data and χ^2/Fisher exact tests for categorical data, as appropriate. Student *t*-tests assuming unequal variances were used to compare mean BMC and BMD at 6, 26, 50, and 74 weeks as well as mean percentage change in BMD from 6 to 74 weeks between both groups. A 2-sided *P* value of <0.05 indicated significance for the primary analyses. A mixed effects linear regression model was used to test for difference in mean BMD at the LS and hip between treatment arms while adjusting for age, BMI, and breastfeeding duration. Mean BMC and BMD at 6, 26, 50, and 74 weeks as well as mean percentage change in BMD from 6 to 74 weeks were compared between women receiving depot medroxyprogesterone acetate (DMPA) and women on no contraception in the Deferred PrEP arm to explore the independent effect of DMPA on BMC and BMD.

Ethical Consideration

The parent study (CAP 016) was conducted in compliance with approval from the South African Health Products Regulatory Authorities. This study was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC/00003767/2022). All maternal participants signed an informed consent that included study follow-up procedures with serial DXA scans.

Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records were identified only by a coded number to maintain subject confidentiality. All records were kept in

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a secured area with access limited to authorized personnel only.

RESULTS

In the CAP016 study, 540 pregnant women without HIV were randomized to either initiate PrEP (n = 271) at baseline (Immediate PrEP arm) or defer PrEP (n = 269) until cessation of breastfeeding (Deferred PrEP arm). Of the 500 pregnant women who remained enrolled in the study at delivery, 300 (60%) returned for their baseline postpartum follow-up visit at 6 weeks, while 52 women first returned at the 26-week visit, 20 women were first seen at the 50-week visit, and 35 women were only seen at the 74-week visit (Fig. 1). Of the 300 women with a 6-week baseline visit, 207 women were also seen at the study end visit at 74 weeks. Overall, 97 women had 1 DXA scan, 91 women had 2 scans, 118 had 3 scans, and 101 had all 4 scans during an 18-month follow-up period. Enrollment commenced in September 2017 and the last participant completed the postpartum 74-week exit visit in December 2021.

The median age of the study population was 23 years, 43% of whom were nulliparous and the majority (64%) came from households with a monthly income <R1200. The mean BMI of the study population was 28, with 34% of the women classified as obese at randomization. Women breastfed for a mean duration of 28 weeks. Baseline characteristics were comparable between the Immediate and Deferred PrEP groups, although women in the Deferred PrEP arm breastfed for a longer period (median 30 vs. 25 weeks) than women in the Immediate PrEP arm (Table 1). Of the 411 women in the postpartum cohort, 305 (74.2%) were on some form of contraception, with similar proportions in the Immediate (76.7%) and Deferred PrEP (71.7%) arms ($P = 0.261$). Most women (89.9%) were on DMPA (Table 1).

BMD and BMC of the Hip and LS by Randomization Arm

For this comparison of BMD and BMC of the hip and LS at the 6-, 26-, 50-, and 74-week time points between women in the Immediate PrEP and Deferred PrEP arms, we included all women with a minimum of 1 DXA scan. At baseline (6 weeks), women in the Deferred PrEP arm had a significantly lower mean BMD and BMC of the LS than women in the Immediate PrEP arm (0.96 vs. 0.99 g/cm^2 and 49.92 vs. 53.49 g) ($P = 0.043$; $P = 0.007$) respectively, but at all other time points, there were no significant differences

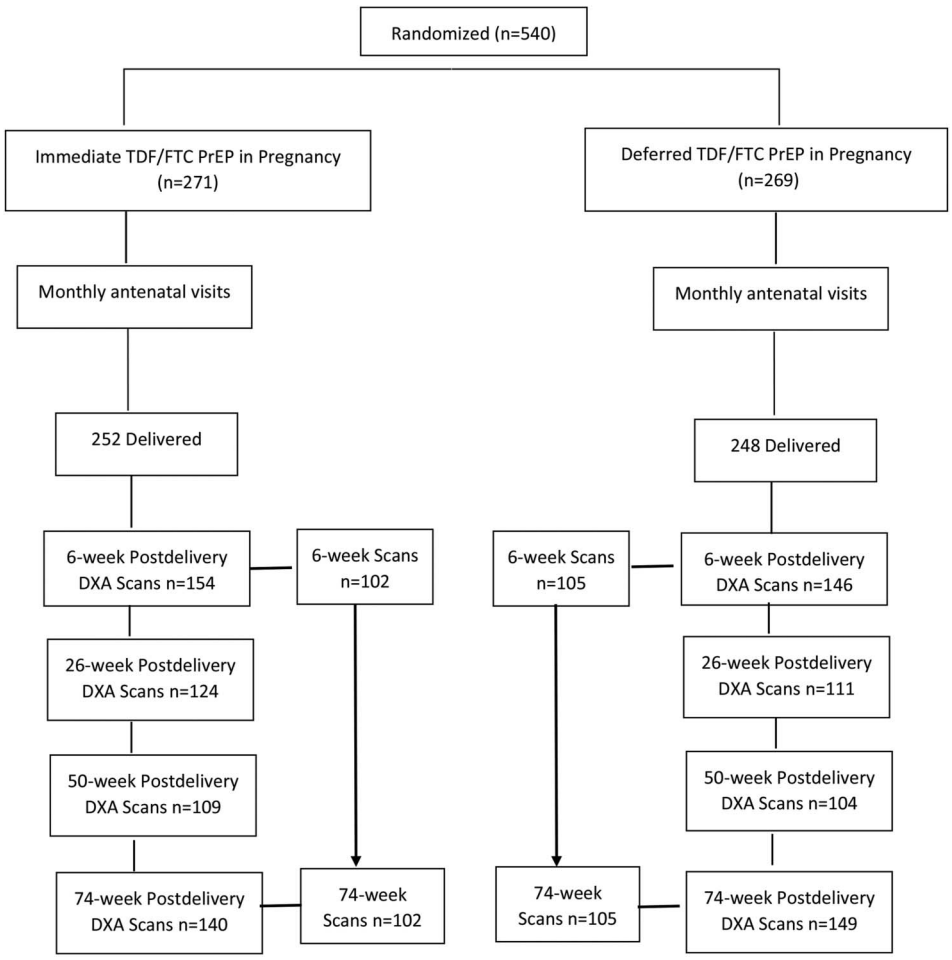


FIGURE 1. Consort diagram of maternal DXA scans by randomization arm. Adjusted means: adjusted for BMI and duration of breastfeeding.

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TABLE 1. Maternal Characteristics by Randomization Arm

Characteristics	Total (N = 411)	Immediate TDF/FTC PrEP Arm (N = 206)	Deferred TDF/FTC PrEP Arm (N = 205)	*P*
Age, yrs	23 (20–27)	24 (21–28)	23 (20–27)	0.349
Median (IQR)				
Weight, kg	70.2 (15.3)	71.7 (15.7)	68.7 (14.9)	0.044
Mean (SD)				
Height, cm	142.5 (47.9)	144.0 (46.4)	140.9 (49.4)	0.506
Mean (SD)				
BMI, kg/m^2	28.1 (5.9)	28.6 (5.8)	27.6 (6.0)	0.098
Mean (SD)				
BMI category (n, %)				
Underweight	6 (1.7)	3 (1.7)	3 (1.7)	0.253
Normal	116 (33.2)	49 (27.8)	67 (38.7)	
Overweight	108 (31.0)	56 (31.8)	52 (30.1)	
Obese	105 (30.1)	60 (34.1)	45 (26.0)	
Severely obese	14 (4.0)	8 (4.6)	6 (3.5)	
Parity (n, %)				
Nulliparous	178 (43.3)	89 (43.2)	89 (43.4)	0.749
Multiparous	233 (56.7)	117 (56.8)	116 (56.6)	
Household income (n, %)				
<R1200	264 (64.2)	126 (61.2)	138 (67.3)	0.217
>R1200	147 (35.8)	80 (38.8)	67 (32.7)	
Employed (n, %)				
Yes	117 (28.5)	61 (29.6)	56 (27.3)	0.662
No	294 (71.5)	145 (70.4)	149 (72.7)	
Breastfeeding duration, wks	27.7 (27.1)	25.2 (26.2)	30.0 (27.7)	0.076
Mean (SD)				
Contraception				
Yes	305 (74.2)	158 (76.7)	147 (71.7)	0.261
No	106 (25.8)	48 (23.3)	58 (28.3)	
Type of contraception				
DMPA	273 (89.5)	139 (87.9)	134 (91.2)	0.593
Implanon	2 (0.7)	1 (0.6)	1 (0.7)	
Nuristerate	29 (9.5)	17 (10.8)	12 (8.7)	
Oral pill	1 (0.3)	1 (0.6)	0	

IQR, interquartile range.

found (Table 2). In this unadjusted analysis, with the exception of a small but significant percentage increase in BMC from 6 to 74 weeks in the Deferred PrEP arm, changes in BMC and BMD of the hip and LS were not significantly different between Immediate PrEP and Deferred PrEP arms (Table 2).

Impact of DMPA Contraception, BMI and Breastfeeding Duration on BMD and BMC of the Hip and LS

In a univariate analysis of women in the Deferred PrEP arm, DMPA use was not associated with BMD and BMC of the hip and LS during the 18-month follow-up period (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/C387). Neither was DMPA associated with percentage change in BMD and BMC of the hip between 6 and 74 weeks postpartum (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/C387). However, the percentage change of BMC at the LS was significantly smaller among women on DMPA (9.9%) when compared with women on no contraception (28.9%) ($P = 0.042$).

Using mixed effects linear regression, BMI was significantly and positively associated with hip BMD (β 0.009; 95% CI: 0.007 to 0.011) ($P < 0.001$) and hip BMC (β 0.302; 95% CI: 0.194 to 0.409) ($P < 0.001$). BMI was also positively associated with LS BMD (β 0.007; 95% CI: 0.005 to 0.009) ($P < 0.001$) and BMC (β 0.368; 95% CI: 0.187 to 0.549) ($P < 0.001$) (see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/C387). Breastfeeding duration was negatively associated with hip BMD (β −0.001; 95% confidence interval (CI): −0.001 to −0.00002) ($P = 0.041$) and LS BMC (β −0.038; 95% CI: −0.075 to −0.0002) ($P = 0.049$). Adjusting for confounding factors (breastfeeding duration and BMI), mean measurements of BMD and BMC with 95% confidence intervals at the hip and LS were not significantly different between the Immediate PrEP and Deferred PrEP arms at all time points (Fig. 2).

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TABLE 2. Mean Difference in BMD and BMC of Hip and LS Between Randomization Arms at 6, 26, 50, and 74 wks and Change in BMD and BMC Between 6 and 74 wks

	Deferred TDF/FTC PrEP Arm		Immediate TDF/FTC PrEP Arm			
	n	Mean (SD)	n	Mean (SD)	Mean Difference (95% CI) Immediate Arm–Deferred Arm	*P*
BMD of hip, g/cm^2						
6 wks	146	0.93 (0.12)	154	0.94 (0.12)	0.01 (−−0.02 to 0.04)	0.426
26 wks	111	0.89 (0.12)	124	0.91 (0.14)	0.02 (−0.01 to 0.06)	0.164
50 wks	104	0.90 (0.13)	109	0.93 (0.13)	0.03 (−0.01 to 0.06)	0.126
74 wks	149	0.91 (0.13)	140	0.92 (0.12)	0.004 (−0.026 to 0.033)	0.809
% change 6–74 wks	105	−2.21 (5.54)	102	−1.70 (4.74)	0.51 (−0.90 to 1.93)	0.475
BMD of lumbar spine, g/cm^2						
6 wks	145	0.96 (0.12)	154	0.99 (0.11)	0.03 (0.001 to 0.05)	0.043
26 wks	112	0.94 (0.10)	125	0.97 (0.11)	0.04 (−0.01 to 0.06)	0.007
50 wks	103	0.97 (0.11)	110	0.99 (0.12)	0.02 (−0.01 to 0.05)	0.182
74 wks	149	0.96 (0.16)	141	0.99 (0.24)	0.03 (−0.02 to 0.08)	0.194
% change 6–74 wks	104	1.37 (5.44)	102	−0.33 (11.08)	−1.70 (−4.09 to 0.69)	0.162
BMC of hip, g						
6 wks	146	27.39 (8.55)	154	28.61 (9.13)	1.23 (−0.79 to 3.24)	0.232
26 wks	111	24.38 (5.55)	124	27.10 (7.93)	2.72 (0.94 to 4.50)	0.003
50 wks	104	25.07 (5.13)	110	26.31 (5.24)	1.24 (−0.16 to 2.64)	0.082
74 wks	149	25.39 (6.16)	140	26.03 (5.76)	0.64 (−0.74 to 2.03)	0.360
% change 6–74 wks	105	−4.13 (20.06)	102	−1.39 (17.89)	2.74 (−2.47 to 7.96)	0.301
BMC of lumbar spine, g						
6 wks	145	49.92 (11.38)	154	53.49 (11.51)	3.58 (0.97 to 6.19)	0.007
26 wks	112	49.70 (9.93)	125	52.11 (11.07)	2.42 (−0.29 to 5.12)	0.079
50 wks	103	51.28 (11.02)	109	55.13 (11.88)	3.85 (0.74 to 6.96)	0.015
74 wks	149	51.84 (11.29)	141	54.29 (11.95)	2.45 (−0.23 to 5.14)	0.073
% change 6–74 wks	104	12.72 (35.69)	103	3.05 (19.35)	−9.67 (−17.55 to −1.79)	0.016

TFV-DP Dose Effect on Hip and LS BMD

Of 260 women randomized to the Immediate PrEP arm in the CAP016 study, 217 (83.5%) had detectable tenofovir (TFV) during pregnancy, 71 had <200 fmol/punch, 47 had TFV between 200 and 400 fmol/punch, 57 had TFV between 400 and 600 fmol/punch, and 42 had TFV more than 600 fmol/punch. In a mixed effects regression model after adjusting for age, BMI, and breastfeeding duration, there was no overall effect of the different levels of TFV-DP on BMD of the hip ($P = 0.231$) (Fig. 3A). Similarly, there was no significant association between TFV-DP level and BMD of the LS ($P = 0.277$) (Fig. 3B).

DISCUSSION

There were no significant differences in BMD and BMC at the hip and LS of postpartum women randomized to the Immediate PrEP arm and exposed to TDF/FTC PrEP during pregnancy and postpartum women randomized to the Deferred PrEP arm and not exposed to TDF/FTC PrEP during pregnancy and lactation. A small but nonsignificant percentage decrease (<3.0%) in BMD and BMC at the hip was observed between 6 and 74 weeks in both treatment arms. Longer breastfeeding duration was significantly associated with a lower BMD at the hip and lower BMC of the LS. A higher BMI was independently and consistently associated with higher BMD and BMC at the hip and LS between 6 and 74 weeks. In a mixed effects regression model after adjusting for age, BMI, and breastfeeding duration, there was no overall dose–effect of TFV-DP on BMD at the hip and LS.

The lack of association between TFV exposure and BMD at the hip and LS in our African breastfeeding population is inconsistent with findings reported for other population groups. In studies of adult populations that included heterosexual men and women exposed to TDF-PrEP, there were small but significant changes in BMD at the hip and LS.[13–15] The HPTN 069/ACTG A5305 trial reported a difference in median percentage change in BMD at the hip at 48 weeks between PrEP arms but no differences were found in BMD at the spine between the 2 groups.[19]

Consistent with our findings, a randomized control trial (RCT) of TDF/FTC-PrEP use among young healthy African women in Uganda and Zimbabwe (Voice Study) revealed no significant differences in percentage change in BMD for 48 weeks between PrEP and placebo groups.[14] However, after considering the low product adherence in this study, the authors demonstrated a small but significant decrease in BMD at the LS and hip from baseline to 48 weeks among a subset

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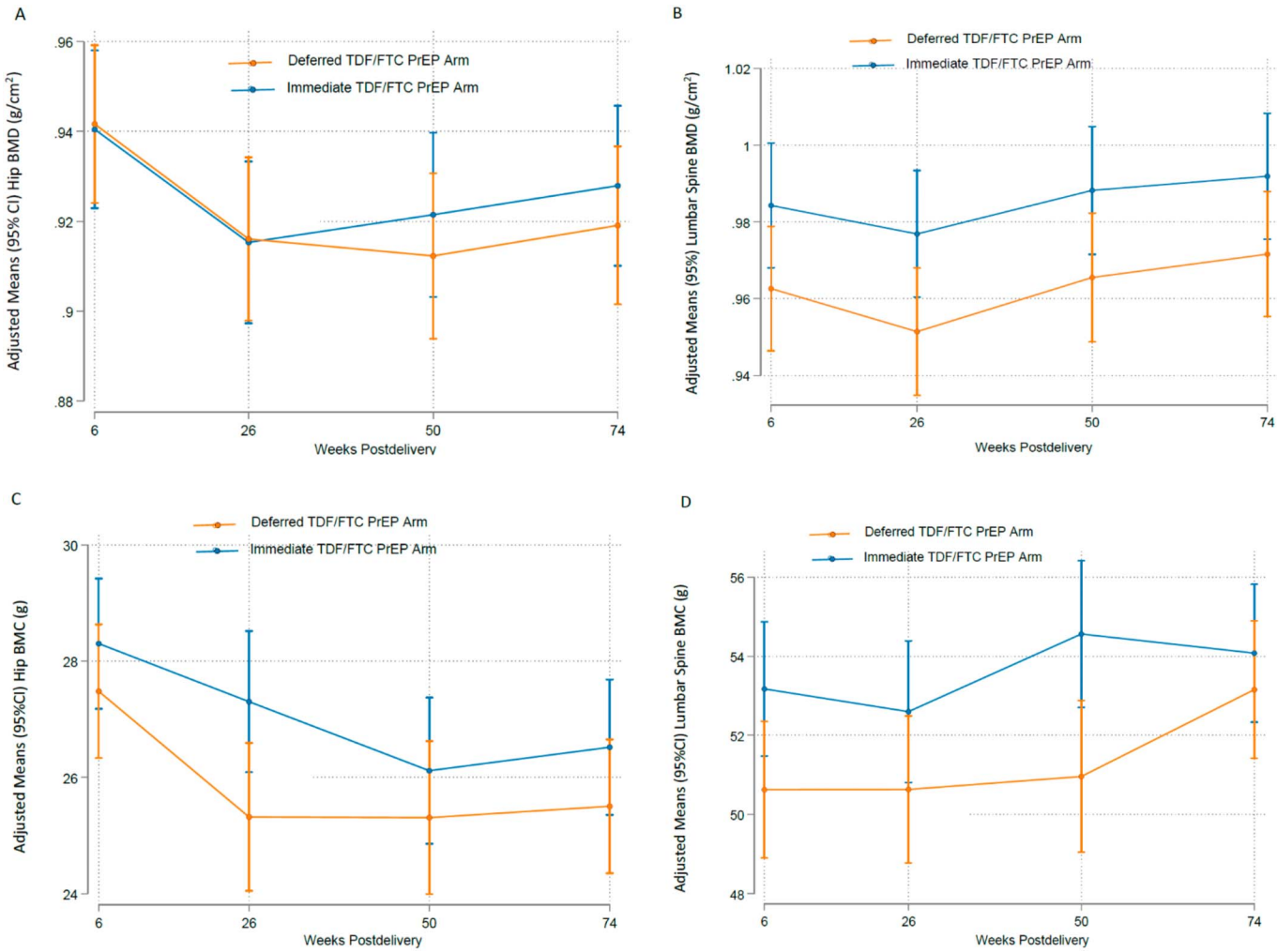


FIGURE 2. Covariate adjusted means (95% CI) for BMD at the hip (A) and LS (B) and BMC at the hip (C) and LS (D) at 6, 26, 50, and 74 weeks postpartum by randomization arm. Adjusted means: adjusted for BMI and duration of breastfeeding.

of women with detectable levels of TFV in comparison with the placebo arm. In our primary analysis, we did not observe significant differences in BMD and BMC of the hip and spine of women in TDF-PrEP exposed and unexposed arms. And in an exploratory analysis, there was no distinct relationship between BMD of the hip and spine and varying levels of TFV-DP detected during pregnancy, suggesting no impact of TDF-PrEP on the bone of breastfeeding women even among women with higher adherence to PrEP. BMD of the hip at all time points between 6 and 74 weeks postpartum among women in the Deferred PrEP (TDF unexposed) arm was not significantly different from that for women with the highest TFV concentrations detected during pregnancy. Studies describing the effect of TDF-PrEP during pregnancy on maternal BMD are limited. In the only other study of TDF-PrEP and BMD of postpartum women, women using PrEP during pregnancy had a higher decline in BMD than women who were never pregnant and not exposed to PrEP. In addition, there was no significant difference in BMD loss between pregnant women who used PrEP and pregnant women who did not use PrEP.[16] These findings are suggestive that pregnancy itself and not TDF-PrEP was associated with bone loss and supported by other studies that describe the high calcium demand during pregnancy as an explanation for the resulting bone resorption.[10,11]

In addition to pregnancy, evidence suggests that breastfeeding is also associated with a decrease in BMD and an increased risk of osteoporosis in later life.[10,11,18,20,21] Bone turnover is markedly increased (up to 35%) during the first 6 months of breastfeeding and 4%–6% of bone loss can occur because of calcium loss in breast milk and a hypoestrogenic state.[22] A longer breastfeeding duration in our study significantly correlated with lower BMD of the hip and lower BMC of the LS. The BMD of the hip and BMC of the LS were consistently lower in women in the Deferred PrEP arm (PrEP Unexposed) than women in the Immediate PrEP arm (PrEP exposed) most likely because women in the Immediate PrEP arm cease breastfeeding earlier to avoid continued PrEP

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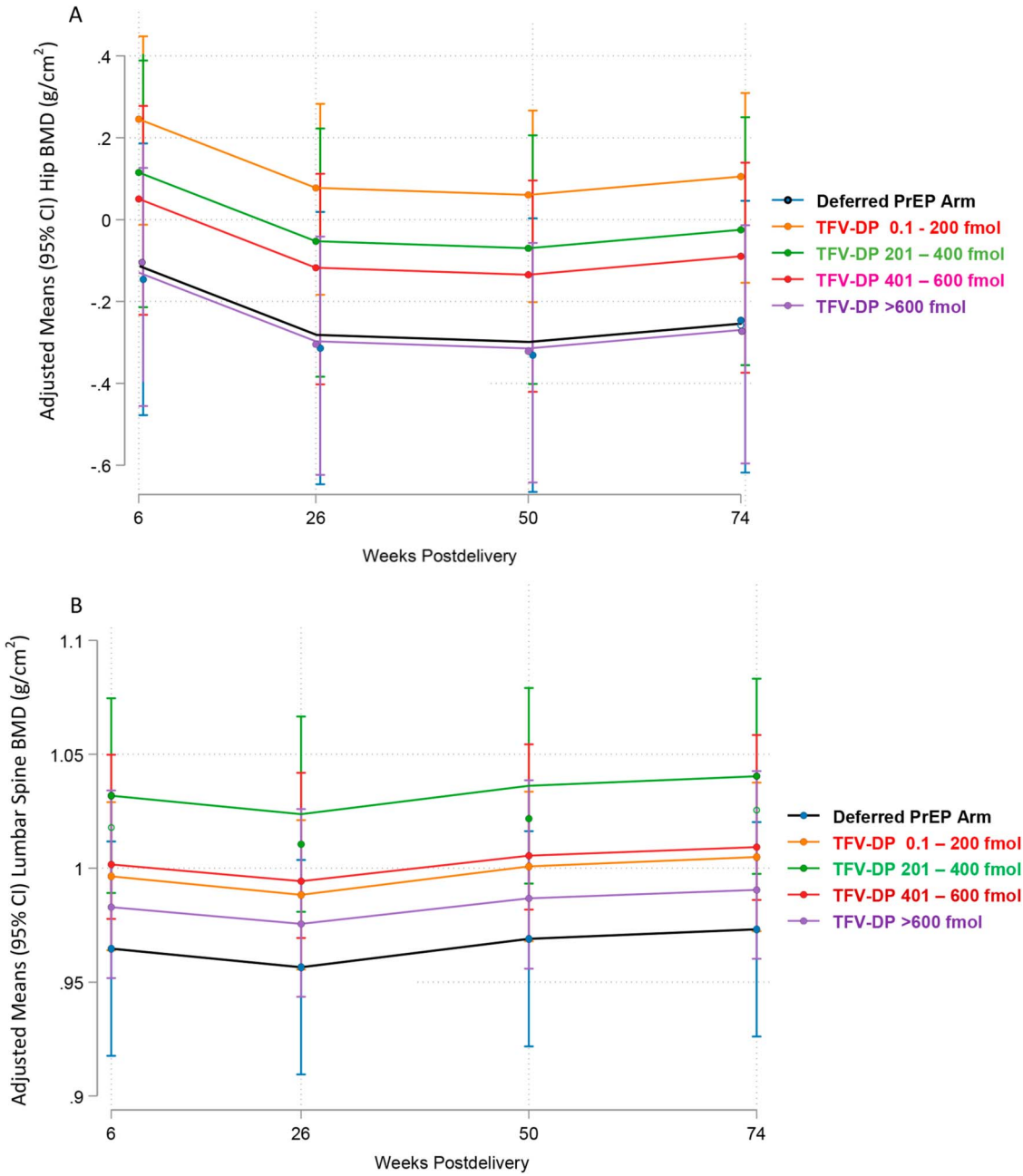


FIGURE 3. Covariate adjusted means (95% CI) for BMD at the hip (A) and LS (B) at 6, 26, 50, and 74 weeks postpartum by TFV-DP levels and deferred PrEP randomization arm. Adjusted means: adjusted for BMI and duration of breastfeeding.

use. We further observed a more rapid recovery rate in BMD of the hip from 26 weeks in the Immediate PrEP arm when compared with 50 weeks in the Deferred PrEP arm. Similarly, Shaki et al[23] in a low socioeconomic setting also found the period of lactation inversely correlated with BMD for LS ($\beta = -0.0812$, $P = 0.0012$) and BMD of femoral neck ($\beta = -0.033$, $P = 0.0031$). In an observational cohort study in Uganda, Nabwire et al,[24] compared BMD among breastfeeding women living with HIV and initiated TDF-emtricitabine and efavirenz as the standard of care treatment regimen with breastfeeding women without HIV. This study also reported a consistent decrease in BMD during breastfeeding across both study groups.

The mean baseline BMI in our healthy African study population without HIV was 28 (World Health Organization classification of overweight or preobesity) and 65% of the study population was overweight or obese. As demonstrated in other study populations, a higher BMI was independently associated with higher BMD of the hip and LS across all postpartum visits for African women without HIV in our study.[25]

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Strengths of the Study

To the best of our knowledge, this is the first study to report a 74-week longitudinal evaluation of BMD among breastfeeding African women without HIV who were randomized to immediate PrEP exposure during pregnancy or deferred PrEP exposure until breastfeeding cessation. As an exploratory analysis, we further evaluated the effect of TDF-PrEP through an objective measure of adherence to the daily oral PrEP regimen that involved TFV measured in DBSs at 2 antenatal visits among women randomized to the Immediate PrEP arm in the CAP016 RCT.

Limitations

Our main limitation in this study is the small sample size that was evaluable at the end of the follow-up period. In addition, study follow-up continued through the COVID-19 pandemic but the schedule of follow-up visits had to be adjusted to mitigate COVID-19 risk. As a result, up to 52% of the study population who had enrolled in the CAP016 RCT had not returned after delivery or did not return for all visits resulting in missing data. And second, although the primary analysis was not intended as a per protocol analysis, there was a high proportion of women in the Immediate arm who had undetectable or low levels of TFV indicating poor adherence to PrEP. We only had <10% of the population with TFV levels exceeding 400 femtomoles/punch to confirm the true effect of the TDF-PrEP regimen on BMD.

CONCLUSIONS

In conclusion, after adjusting for breastfeeding and BMI, TFV disoproxil fumarate when given in combination with FTC as pre-exposure prophylaxis during pregnancy had no deleterious effect on BMD and BMC at the hip and LS of African breastfeeding women. Our study provides further reassuring evidence of the safety of TDF/FTC-PrEP for pregnant and breastfeeding women.

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REFERENCES

1. Doherty M, Ford N, Vitoria M, et al. The 2013 WHO guidelines for antiretroviral therapy: evidence-based recommendations to face new epidemic realities. *Curr Opin HIV AIDS*. 2013;8:528–534.
2. Maggiolo F, Rizzardini G, Raffi F, et al. Bone mineral density in virologically suppressed people aged 60 years or older with HIV-1 switching from a regimen containing tenofovir disoproxil fumarate to an elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide single-tablet regimen: a multicentre, open-label, phase 3b, randomised trial. *Lancet HIV*. 2019;6:e655–e666.
3. Bloch M, Tong WW, Hoy J, et al. Switch from tenofovir to raltegravir increases low bone mineral density and decreases markers of bone turnover over 48 weeks. *HIV Med*. 2014;15:373–380.
4. Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. *Lancet HIV*. 2020;7:e666–e676.
5. Bedimo R, Cutrell J, Zhang S, et al. Mechanisms of bone disease in HIV and hepatitis C virus: impact of bone turnover, tenofovir exposure, sex steroids and severity of liver disease. *AIDS*. 2016;30:601–608.
6. Moyle GJ, Hardy H, Farajallah A, et al. Changes in bone mineral density after 96 weeks of treatment with atazanavir/ritonavir or lopinavir/ritonavir plus tenofovir DF/emtricitabine in treatment-naive patients with HIV-1 infection: the CASTLE body composition substudy. *J Acquir Immune Defic Syndr*. 2015;68:40–45.
7. McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: aids Clinical Trials Group A5224s, a sub study of ACTG A5202. *J Infect Dis*. 2011;203:1791–1801.
8. Grigsby IF, Pham L, Mansky LM, et al. Tenofovir treatment of primary osteoblasts alters gene expression profiles: implications for bone mineral density loss. *Biochem Biophys Res Commun*. 2010;394:48–53.
9. Mgodi NM, Kelly C, Gati B, et al. Factors associated with bone mineral density in healthy African women. *Arch Osteoporos*. 2015;10:206.
10. Sowers M. Pregnancy and lactation as risk factors for subsequent bone loss and osteoporosis. *J Bone Miner Res*. 1996;11:1052–1060.
11. Pitkin RM. Calcium metabolism in pregnancy and the perinatal period: a review. *Am J Obstet Gynecol*. 1985;151:99–109.
12. Stranix-Chibanda L, Tierney C, Sebikari D, et al. Impact of postpartum tenofovir-based antiretroviral therapy on bone mineral density in breastfeeding women with HIV enrolled in a randomized clinical trial. *PLoS One*. 2021;16:e0246272.
13. Mulligan K, Glidden DV, Anderson PL, et al. Effects of emtricitabine/tenofovir on bone mineral density in HIV-negative persons in a randomized, double-blind, placebo-controlled trial. *Clin Infect Dis*. 2015;61:572–580.
14. Mirembe BG, Kelly CW, Mgodi N, et al. Bone mineral density changes among young, healthy African women receiving oral tenofovir for HIV preexposure prophylaxis. *J Acquir Immune Defic Syndr*. 2016;71:287–294.
15. Kasonde M, Niska RW, Rose C, et al. Bone mineral density changes among HIV-uninfected young adults in a randomised trial of pre-exposure prophylaxis with tenofovir-emtricitabine or placebo in Botswana. *PLoS One*. 2014;9:e90111.
16. Zewdie K, Kiweewa FM, Ssebuliba T, et al. The effect of daily oral PrEP use during pregnancy on bone mineral density among adolescent girls and young women in Uganda. *Front Reprod Health*. 2023;5:1240990.
17. Moodley D, Lombard C, Govender V, et al. Pregnancy and neonatal safety outcomes of timing of initiation of daily oral tenofovir disoproxil fumarate and emtricitabine pre-exposure prophylaxis for HIV prevention (CAP016): an open-label, randomised, non-inferiority trial. *Lancet HIV*. 2023;10:e154–e163.
18. Stranix-Chibanda L, Anderson PL, Kacanek D, et al. Tenofovir diphosphate concentrations in dried blood spots from pregnant and postpartum adolescent and young women receiving daily observed pre-exposure prophylaxis in sub-Saharan Africa. *Clin Infect Dis*. 2021;73:e1893–e1900.
19. Brown TT, Yuhas K, Mayer KH, et al. Bone changes with candidate PrEP regimens containing tenofovir disoproxil fumarate and/or maraviroc and/or emtricitabine in US men and women: HPTN 069/ACTG A5305. *J Antimicrob Chemother*. 2022;77:500–506.
20. Scioscia MF, Vidal M, Sarli M, et al. Severe bone microarchitecture impairment in women with pregnancy and lactation-associated osteoporosis. *J Endocr Soc*. 2021;5:bvab031.
21. Ferreira LB, Tirapeli KG, Silva CC, et al. Lumbar spine bone mineral density in women breastfeeding for a period of 4 to 6 months: systematic review and meta-analysis. *Int Breastfeed J*. 2023;18:68.
22. Nabwire F, Hamill MM, Fowler MG, et al. Biochemical markers of calcium and bone metabolism during and after lactation in Ugandan women with HIV on universal maternal antiretroviral therapy. *J Bone Miner Res*. 2023;38:1296–1311.
23. Shaki O, Gupta TP, Rai SK, et al. Does parity and duration of lactation have any effect on the bone mineral density of the femur and lumbar spine in Indian women? A cross-sectional study from the Northeast region of India. *J Fam Med Prim Care*. 2021;10:2886–2892.

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24. Nabwire F, Prentice A, Hamill MM, et al. Changes in bone mineral density during and after lactation in Ugandan women with HIV on tenofovir-based antiretroviral therapy. *J Bone Miner Res*. 2020;35:2091–2102.

25. Morin S, Leslie WD, Manitoba Bone Density Program. High bone mineral density is associated with high body mass index. *Osteoporos Int*. 2009;20:1267–1271.

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