Intramuscular depot medroxyprogesterone acetate accentuates bone loss associated with tenofovir disoproxil fumarate-containing antiretroviral therapy initiation in young women living with HIV (the BONE: CARE study): a prospective cohort study in Uganda

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Summary

Background Tenofovir disoproxil fumarate (TDF) and intramuscular depot medroxyprogesterone acetate (DMPA-IM) are independently associated with reduced bone mineral density (BMD). We aimed to assess the combined effects of DMPA-IM use and TDF initiation on BMD in young adult women living with HIV over two years, compared with age-matched people without HIV.

Methods Th BONE: CARE study was a prospective cohort study that recruited women aged 18–35 years from 11 HIV care and general health facilities in Kampala, Uganda. The participants were classified into four groups on the basis of their combination of HIV status, TDF use, and DMPA-IM use, as follows: women living with HIV initiating TDF-containing antiretroviral therapy (ART) with DMPA-IM (HIV positive, DMPA positive, and TDF positive); women living with HIV using DMPA-IM but not eligible for ART as per local guidelines at the time of enrolment into the study (HIV positive, DMPA positive, and TDF negative); women living with HIV initiating TDF-containing ART without DMPA-IM (HIV positive, DMPA negative, and TDF positive); and controls without HIV using non-hormonal contraceptives (HIV negative, DMPA negative, and TDF negative). BMD of the lumbar spine, total hip, and femoral neck were measured using semiannual dual-energy x-ray absorptiometry at enrolment and at intervals every 6 months thereafter. We assessed percentage change in mean BMD.

Findings Between March 30, 2016, and Oct 19, 2017, we enrolled 265 women living with HIV initiating ART (159 DMPA-IM users and 106 non-hormonal contraceptive users), 187 women living with HIV using DMPA-IM but not ART, and 69 controls without HIV. Mean age was 26·1 years (SD 4·2). BMD declined significantly from baseline in women living with HIV on TDF with versus without DMPA-IM at the lumbar spine (–3·406% [95% CI –3·969 to –2·844] *vs* –1·111% [–1·929 to –0·293]; p<0·0001), total hip (–3·856% [–4·449 to –3·264] *vs* –1·714% [–2·479 to –0·949]; p=0·0002), and femoral neck (–4·422% [–5·078 to –3·766] *vs* –1·999% [–3·022 to –0·976]; p=0·0002), increased in controls at the lumbar spine (1·5% change), and remained unchanged at total hip and femoral neck (–0·1% change). Concurrent use of TDF and DMPA-IM resulted in significantly greater BMD decline (p<0·0001) than TDF alone (lumbar spine –2·677% [95% CI –3·743 to –1·611]; p<0·0001; total hip –2·518% [–3·575 to –1·461]; p<0·0001; and femoral neck –2·907 [–4·132 to –1·683]; p<0·0001) or than controls (lumbar spine –4·970% [–6·391 to –3·549]; p<0·0001; total hip –4·151% [–5·579 to –2·724]; p<0.0001; and femoral neck –4·773% [–6·424 to –3·122]; p<0·0001)

Interpretation Concomitant DMPA-IM use resulted in a doubling of BMD loss in women living with HIV initiating TDF-containing ART. Identification of safer contraceptive and bone-sparing ART options should be prioritised for optimal care of women living with HIV.

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Introduction

In sub-Saharan Africa, the HIV burden remains high, particularly among women,[1] many of whom are living longer because of expanded access to antiretroviral therapy (ART).[2,3] Current treatment options, such as tenofovir disoproxil fumarate (TDF)-containing ART with simpler once-a-day dosing regimens promise even further increases in life expectancy. These trends suggest that many of the women currently living with HIV infection will live to experience menopause and its possible sequelae, including osteoporosis. Because of prolonged exposure to HIV and to ART, fragility fractures

Research in context

Evidence before this study

Antiretroviral therapy (ART) initiation is associated with rapid acceleration of bone turnover and a decline in bone mineral density (BMD). Although highly potent and safe, tenofovir disoproxil fumarate (TDF) causes greater BMD loss than non-TDF containing regimens, particularly in the first 1–2 years of use. Similarly, there is a strong body of evidence from longitudinal data that shows that intramuscular depot medroxyprogesterone acetate (DMPA-IM) negatively affects BMD in current users. DMPA-IM is known to cause bone loss to such an extent as to warrant a US Food and Drug Administration so-called black-box warning. Because of the hypo-oestrogenemic effects of DMPA, women using DMPA have a lower BMD than non-users with the greatest bone loss occurring in the first few years of use, which is more pronounced in younger women. Although DMPA-IM and TDF have independently been shown to negatively affect BMD in previous studies, their combined effect is not known. We searched the PubMed database for research papers, systematic reviews, and meta-analyses published in English between January 1, 1990 and August 1, 2014 with the search terms ''bone mineral density'' AND ''HIV'' OR ''tenofovir disoproxil fumarate'' OR ''depot medroxyprogesterone acetate''. Additionally, we looked up unpublished reports, conference presentations, and ongoing studies via the Google search engine. Although several studies had examined TDF in people living with HIV, the majority primarily included men (generally >85%) with relatively little known about the effects of TDF on bone in women. Furthermore, there was scarce data in any geographical setting regarding longitudinal changes in BMD in people living with HIV not treated with ART, nor was there data from resource-limited settings where both TDF and DMPA-IM are very commonly used together, which exposes millions of women living with HIV to their negative effects on BMD.

Added value of this study

This study addresses an important gap highly relevant to the management of HIV in young adult women. The study has important public health implications in wide geographical areas that remain understudied. BMD in young adulthood, which is the time of peak bone-mass attainment, accounts for approximately 50% of BMD variance at age 65 years and is therefore a major, potentially modifiable, risk factor for fragility fractures in older populations. It is indeed crucial to identify risk factors that might affect peak bone mass to decrease the risk of future factures.

Implications of all the available evidence

We provide the first evidence of the combined deleterious effect of DMPA-IM use and TDF-containing ART initiation on BMD. ART initiation with a TDF-containing regimen in a cohort of young adult ART-naive women living with HIV was associated with significant declines in BMD. Concurrent use of DMPA-IM and TDF resulted in a doubling of BMD loss compared with use of TDF alone. Therefore, as the HIV treatment landscape continues to evolve, treatment choices and management practices that balance optimal efficacy with improved long-term safety are needed for women living with HIV using DMPA-IM hormonal contraception.

are likely to become a major source of morbidity and mortality among people living with HIV.[4,5]

People living with HIV have accelerated bone loss, higher rates of osteopenia and osteoporosis, and subsequent fractures than the general population.[6] The underlying mechanisms of accelerated bone loss are multifactorial and include both traditional and HIV-specific risk factors.[7] It is unclear how much of the bone loss is caused by HIV infection per se or the consequences of ART. With ART initiation, bone turnover accelerates with bone resorption outstripping bone formation, accounting for the decrease in bone mineral density (BMD).[8] Of the different antiretroviral drugs, the potential effect of TDF is particularly concerning. Although highly potent and safe, TDF is associated with decreased BMD,[9] fractures,[5] and renal tubular effects. With treatment initiation, TDF causes greater BMD loss than non-TDF-containing regimens, particularly in the first 1–2 years of use.[9]

Among women of childbearing age, the choice of contraception can also affect bone health. Of concern is the concurrent use of intramuscular depot medroxy-progesterone acetate (DMPA-IM) and TDF. DMPA-IM is a highly effective and well accepted progesterone-based contraceptive.[10] In women living with HIV, DMPA-IM does not have pharmacokinetic interactions with antiretroviral drugs.[11] However, DMPA-IM induces a hypo-oestrogenic state, accelerating bone turnover, leading to bone loss[12,13] and an increased risk of fractures.[14] Women using DMPA-IM have a lower BMD than non-users, with the greatest BMD loss occurring particularly in younger women and in the first few years of use.[15]

Given that both DMPA-IM and TDF are widely used in resource-limited settings, there is concern that concurrent use of these two agents might potentiate the effects of the other on BMD. This could lead to increased morbidity related to earlier bone loss, and fragility fractures among women living with HIV. Although both drugs reduce BMD, no studies have examined their combined effects.[16] The BONE: Contraception and AntiRetroviral Effects (CARE) study is the first longitudinal assessment of the combined effect of DMPA-IM and TDF on BMD among women living with HIV. Our primary objectives were to determine the combined effect of DMPA-IM use and TDF initiation on BMD and to determine whether BMD loss with TDF-containing ART initiation over a 2-year follow-up period was greater with DMPA-IM use among young women living with HIV.

Methods

Study population

The BONE: CARE study was an observational prospective cohort study done at the Makerere University–Johns Hopkins University Research Collaboration in Kampala, Uganda. Between March 30, 2016 and Oct 19, 2017, we sequentially recruited women living with HIV aged 18–35 years and controls without HIV from 11 HIV care and general health facilities in Kampala. The participants were classified on the basis of their combination of HIV status, DMPA-IM use, and intention to initiate TDF-containing ART, resulting in four groups: women living with HIV initiating TDF-containing ART with DMPA-IM (HIV positive, DMPA positive, and TDF positive); women living with HIV using DMPA-IM but not eligible for ART per local guidelines at the time of enrolment into the study (HIV positive, DMPA positive, and TDF negative);[17] women living with HIV initiating TDF-containing ART without DMPA-IM (HIV positive, DMPA negative, and TDF positive); and controls without HIV using non-hormonal contraceptives (HIV negative, DMPA negative, and TDF negative). All women living with HIV were ART naive at enrolment. Study entry criteria included: age between 18 years and 35 years and documented HIV infection status. DMPA-IM users (groups 1 and 2) were either new or current DMPA-IM users users regardless of the duration of previous use. Non-hormonal groups 2 and 4 (with and without HIV, respectively) comprised current users of the TCu380A copper intrauterine device or condoms who had not used DMPA-IM or any other hormonal method for more than 3 consecutive months in the previous 2 years. All women living with HIV were either eligible (CD4 ≤500 cells/μl or WHO stage ≥3), or ineligible (CD4 ≥500 cells/μl) for ART initiation at screening. Regardless of their HIV infection status, women were excluded if they had been pregnant or breastfeeding in the past 6 months before enrolment, had intented to become pregnant during the 2-year study, or had a pre-existing medical condition known to affect bone metabolism.[18]

ART was provided by primary health-care facilities in accordance with the Uganda National ART guidelines at the time that recommended initiation of TDF, lamivudine and efavirenz, or nevirapine for people living with HIV with a CD4 count of up to 500 cells/μL or WHO stage 3 or higher.[17] In February, 2017, new guidelines were implemented in Uganda that eliminated all restrictions on ART initiation among people living with HIV. By October, 2017, all participants in the HIV positive, DMPA positive, and TDF negative group had been initiated on TDF-containing ART that modified their exposure classification to the HIV positive, DMPA positive, and TDF positive group. The protocol was amended to follow up these women for 2 years after ART initiation, and to have their semiannual dual-energy x-ray absorptiometry (DXA) scheduling modified to match the ART initiation dates. Participants were encouraged to receive their contraceptive services from the study clinic whenever possible.

Study procedures

Information regarding sociodemographic characteristics, reproductive history, medical conditions, physical activity, and anthropometry was obtained at baseline and at months 1, 3, 6, 9, 12, 15, 18, 21, and 24. Details are provided in the baseline analysis of this study population.[18]

BMD of the lumbar spine (L1–L4), total hip, and femoral neck were measured at baseline, and thereafter every 6 months for 2 years using DXA.[19] Participants with low BMD were given supplements of calcium lactate (300 mg) and vitamin D3 (800 IU).[20] Details on the DXA software, Z score estimation, and quality-control measures have been previously described.[18]

A point-of-care urine human chorionic gonadotropin test was done for each participant before each DXA scan. Viral load testing was done at baseline and at months 12 and 24. Details on viral load testing and CD4 cell counts have been previously described.[18]

Ethical considerations

The protocol was approved by the Uganda Virus Research Institute Ethics Committee (GC/127/16/09/524), Uganda National Council for Science and Technology (HS 1942), and the Human Research Ethics Committee at the University of the Witwatersrand, South Africa (M150858). Written informed consent for study participation was obtained from all participants.

Statistical analysis

The BONE: CARE study was designed as a 2-year follow-up study with three inter-related but separate substudies. Sample size estimations were done for each substudy using empirical BMD values from previous studies. Estimates of sample size were done for various anticipated differences in mean BMD values before and after baseline. All estimates were based on a type-1 error (α) of 0·05, power (1–β) of 0·9, and attrition rate (loss to follow-up, pregnancy, and discontinuation of contraception) of 20% over a 2-year period.

Baseline characteristics were compared among the study groups using Pearson's χ^2 test or Fisher's exact test for categorical variables and one-way analysis of variance for continuous variables. Primary outcomes were percentage change in mean BMD from baseline to 2 years at the lumbar spine, total hip, and femoral neck. Paired Student *t* tests were used to compare baseline versus postbaseline mean BMD measurements every 6 months. Multiple linear-regression models were used to determine adjusted relative differences in BMD change between baseline and mean postbaseline measures (ie, a difference of differences analysis). Estimates were made comparing women living with HIV using or not using DMPA-IM with controls (HIV

negative, DMPA negative, and TDF negative). Women living with HIV (HIV positive, DMPA positive, and TDF negative) who initiated ART under the test-and-treat guidelines introduced during the study were included in the HIV positive, DMPA positive, and TDF positive group once initiated.

Models were adjusted for age (as a continuous variable), body-mass index (BMI; as a time-varying

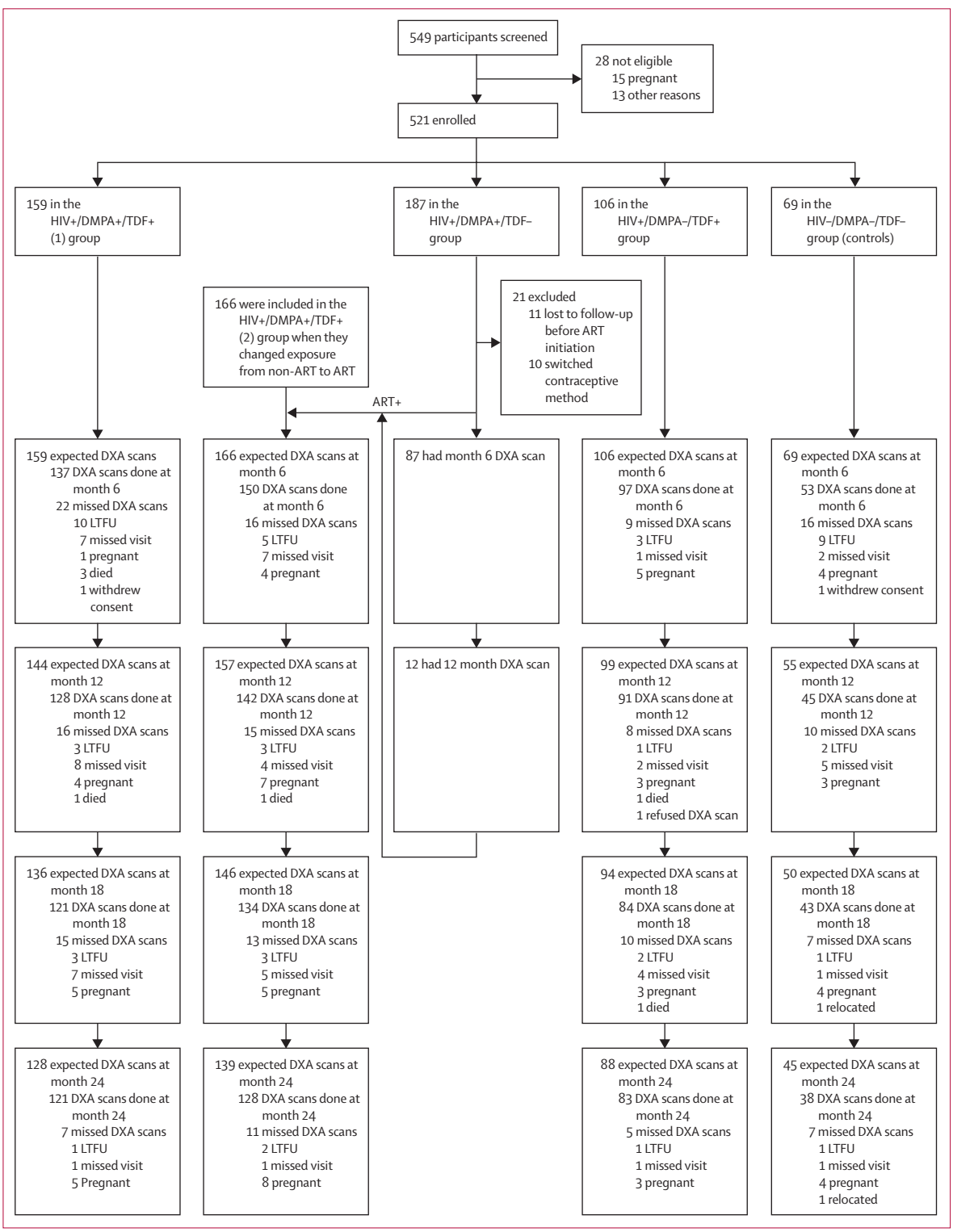

Figure 1: **Participants in the BONE: CARE Study**
One participant in the HIV+/DMPA+/TDF+ (2) group had a missing baseline scan at the lumbar spine and another participant in the same group was missing a baseline scan at the total hip and femoral neck. Women were initiated on ART at different timepoints. Consequently, their data were included at the different timepoints when they changed exposure from non-ART to ART. DMPA=depot medroxyprogesterone acetate. DXA=dual-energy x-ray absorptiometry. HIV+/DMPA+/TDF+ (1)=initially HIV positive, DMPA positive, and TDF positive. HIV+/DMPA+/TDF+ (2)=later HIV positive, DMPA positive, and TDF positive. HIV+/DMPA+/TDF–=HIV positive, DMPA positive, and TDF negative. HIV+/DMPA–/TDF+=HIV positive, DMPA negative, and TDF positive. HIV–/DMPA–/TDF–=HIV negative, DMPA negative, and TDF negative. LTFU=lost to follow-up. TDF=tenofovir disoproxil fumarate.

	Total (n=521)	Women living with HIV initiating TDF-containing ART with DMPA-IM at CD4 ≤500 cells/μL (HIV positive, DMPA positive, and TDF positive; n=159)	Women living with HIV using DMPA-IM but not eligible for ART initiation at CD4 >500 cells/μL (HIV positive, DMPA positive, and TDF negative; n=187)*	Women living with HIV initiating TDF-containing ART with DMPA-IM, including those following test and treat (HIV positive, DMPA positive, and TDF positive; n=325)†	Women living with HIV initiating TDF-based ART without DMPA-IM (HIV positive, DMPA negative, and TDF positive; n=106)	Women not living with HIV and not using DMPA-IM (controls; n=69)	p value‡
Age, years	26·1 (4·2)	26·3 (3·9)	26·2 (4·0)	26·4 (4·0)	26·8 (4·6)	24·4 (4·0)	0·0016
18–24	202 (39%)	58 (36%)	69 (37%)	117 (36%)	41 (39%)	34 (49%)	..
25–35	319 (61%)	101 (64%)	118 (63%)	208 (64%)	65 (61%)	35 (51%)	0·28
Completed education level							
Below secondary	228 (44%)	76 (48%)	100 (53%)	168 (52%)	40 (38%)	12 (17%)	..
Secondary and higher	293 (56%)	83 (52%)	87 (47%)	157 (48%)	66 (62%)	57 (83%)	<0·0001
Marital status							
Not married	224 (43%)	68 (43%)	76 (41%)	136 (42%)	52 (49%)	28 (41%)	..
Married	297 (57%)	91 (57%)	111 (59%)	189 (58%)	54 (51%)	41 (59%)	0·54
Earns income	362 (69%)	111 (70%)	141 (75%)	238 (73%)	76 (72%)	34 (49%)	0·0010
Median monthly income, US$	40·7 (27·1–70·6)	40·7 (27·1–81·4)	40·7 (27·1–67·8)	40·7 (27·1–65·1)	40·7 (27·1–71·9)	54·3 (40·7–81·4)	0·098
Proportion currently using DMPA-IM	177 (79%)	82 (74·5%)	95 (78%)	168 (76%)	0	0	..
Median duration of DMPA-IM use, months	24 (12–48)	24 (12–48)	24 (9–48)	24 (12–48)	NA	NA	0·94
Age at menarche, years	14·2 (1·6)	14·2 (1·8)	14·2 (1·6)	14·2 (1·7)	14·3 (1·4)	14·0 (1·4)	0·86
Ever pregnant	436 (84%)	145 (91%)	174 (93%)	301 (93%)	84 (79%)	33 (48%)	<0·0001
Median parity	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	0 (0–2)	<0·0001
Ever breastfed	390 (75%)	136 (86%)	160 (86%)	280 (86%)	69 (65%)	25 (36%)	<0·0001
Median duration of breast feeding	26 (15–43)	26 (16–43·5)	25·5 (15–42·5)	26 (15·5–44)	26 (12–42)	28 (18–50)	0·99
Currently drinks alcohol	142 (27%)	52 (33%)	59 (32%)	106 (33%)	23 (22%)	8 (12%)	0·0030
Ever smoked	22 (4%)	7 (4%)	9 (5%)	15 (5%)	5 (5%)	1 (1%)	0·69
Current smoker§	12/22 (55%)	4/7 (57%)	6/9 (67%)	9/15 (60%)	2/5 (40%)	0	0·73
Physical activity (minutes per week)¶							
Vigorous (≥75 min)	55/71 (78%)	15/20 (75%)	22/25 (88%)	36/43 (84%)	9/14 (64%)	9/12 (75%)	0·35
Moderate (≥150 min)	169/269 (63%)	46/74 (62%)	63/98 (64%)	102/160 (64%)	32/55 (58%)	28/42 (67%)	0·83
Median CD4 cell count, cells/μL	670 (411–859)	452 (327–605)	851 (754–1024)	709 (454–890)	442 (309–641)	N/A	<0·0001
Body-mass index, kg/m²	24·7 (4·4)	24·8 (4·4)	25·2 (4·6)	25·0 (4·5)	24·3 (4·1)	24·0 (4·1)	0·16
Median viral load, log_{10} copies/mL	4·1 (3·2–4·6)	4·21 (3·56–4·89)	3·90 (2·77–4·40)	4·08 (3·35–4·64)	4·16 (3·29–4·60)	N/A	0·12
Mean BMD, g/cm²							
Lumbar spine	0·938 (0·110)	0·927 (0·106)	0·926 (0·110)	0·923 (0·109)	0·960 (0·118)	0·966 (0·098)	0·0057
Total hip	0·960 (0·115)	0·942 (0·108)	0·954 (0·110)	0·948 (0·109)	0·975 (0·130)	0·995 (0·107)	0·0045
Femoral neck	0·863 (0·116)	0·847 (0·112)	0·855 (0·113)	0·851 (0·113)	0·877 (0·126)	0·896 (0·108)	0·011
Mean BMD Z score							
Lumbar spine	−0·383 (1·131)	−0·502 (1·112)	−0·507 (1·146)	−0·508 (1·138)	−0·236 (1·162)	0·000 (0·985)	0·0031
Total hip	−0·452 (1·120)	−0·628 (1·070)	−0·502 (1·068)	−0·570 (1·076)	−0·394 (1·287)	0·000 (0·985)	0·0011
Femoral neck	−0·409 (1·091)	−0·553 (1·064)	−0·467 (1·042)	−0·521 (1·055)	−0·355 (1·221)	0·000 (0·985)	0·0039
Low BMD Z score by anatomical site (up to −2)							
Lumbar spine	43 (8%)	14 (9%)	21 (11%)	33 (10%)	7 (7%)	1 (1%)	0·077
Total hip	45 (9%)	16 (10%)	16 (9%)	31 (10%)	13 (12%)	0	0·034
Femoral neck	33 (6%)	11 (7%)	12 (6%)	23 (7%)	9 (8%)	1 (1%)	0·30
Low BMD Z score (up to −2) at any of the three sites							
Normal score (2 and higher)	443 (85%)	135 (85%)	152 (81%)	269 (83%)	89 (84%)	67 (97%)	..
Low score (up to −2)	78 (15%)	24 (15%)	35 (19%)	56 (17%)	17 (16%)	2 (3%)	0·018

Data are mean (SD), median (IQR), or proportions unless otherwise stated. TDF=tenofovir disoproxil fumarate. ART=antiretroviral therapy. DMPA-IM=intramuscular depot medroxyprogesterone acetate. BMD=bone mineral density. NA=not applicable. *Participants not eligible for ART initiation at the time (CD4 cell count >500 cells/μL) later initiated ART under the test-and-treat guidelines. †The combined total of women living with HIV who initiated TDF on the basis of ART with DMPA-IM was 325 women (159 eligible for ART before test and treat + 166 initiated on ART under test and treat. ‡Difference in baseline characteristics across groups. §Among women who have ever smoked. ¶Vigorous physical activity over a shorter duration (at least 75 min) had the same health benefits as moderate physical activity done over a longer period of time (at least 150 min); some women contributed to both categories of physical activity.

Table 1: **Baseline characteristics of women enrolled in the BONE: CARE Study**

covariate), and baseline BMD. A mixed-effects regression model was used to estimate the annualised rate of change in BMD within each of the three study groups adjusting for the same aforementioned variables. All the above analyses were done on a prespecified basis and classified by exposure. A post-hoc analysis based on exposure classification was done to assess whether consistent users of DMPA-IM and TDF had more bone loss than inconsistent users. Consistent use of DMPA-IM was defined as receiving two or more injections of DMPA-IM within 1 year or four or more injections in 2 years of follow-up, whereas consistent use of TDF-containing ART was defined as virological suppression (<1000 copies/mL) at both the 12-month and 24-month timepoints. Statistically significant differences between groups were tested at a p value of up to 0·05 and all p values were two sided. Data for women who became pregnant were censured at first positive pregnancy test. All analyses were done using Stata Release 16.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report

Results

Participants were recruited between March 30, 2016, and Oct 19, 2017. Of the 549 women screened, 521 women were enrolled, of which 452 (87%) were women living with HIV and 69 (13%) without HIV (figure 1). Of the women living with HIV, 265 (59%) initiated TDF-containing ART (159 DMPA-IM users and 106 non-hormone users), and 187 (41%) were not eligible for ART at the time of their enrolment. Of the women who were not eligible for ART, 166 (89%) later initiated ART under the revised Uganda test-and-treat policy and continued in the study, 21 (11%) of the original 187 women having been excluded from the analysis because of different reasons (figure 1). The majority (516 [99%]) of women initiated TDF, lamivudine, and efavirenz treatment, with only 1% on TDF, lamivudine, and nevirapine. Two women switched to non-TDF regimens during the course of the study (a switch to abacavir, lamivudine, and atazanavir–ritonavir and abacavir, lamivudine, and efavirenz), but were included in the final analysis. Median time between ART initiation and enrolment was 0 days (IQR 0–2).

Baseline characteristics are shown in table 1. Mean age at baseline was 26·1 years (SD 4·2) and 84% of the women had a history of pregnancy with a median parity of 2 (IQR 1–3). Among DMPA-IM users, the majority (73%) were using DMPA-IM at the time of enrolment with a median duration of 26·0 months (IQR 12–48). Compared with women living with HIV, controls were more likely to be younger, have more years of education, lower parity, and to have never breastfed. There was no difference in baseline viral load between the women living with HIV groups. Women living with HIV had significantly lower baseline BMD at all bone sites than controls (p<0·01). Compared with the control group, a higher proportion of women living with HIV, irrespective of the type of contraceptive use, had lower BMD *Z* scores (*Z* score up to –2·0 at any of the three sites) at enrolment (2·9% *vs* around 16·5%; p=0·018).

BMD at femoral neck and total hip sites among controls did not change over the follow-up period but a slight increase in BMD at the lumbar spine was noted at 6 months, 12 months, and 24 months (p<0·05; figure 2). However, in women living with HIV, BMD at the three sites declined at all timepoints after enrolment. The majority of BMD loss at all sites among women living with HIV initiating TDF-containing ART occurred within the first 12 months of treatment (figure 2). Greater declines in BMD occurred among concurrent users of DMPA-IM and TDF than in users on TDF-containing

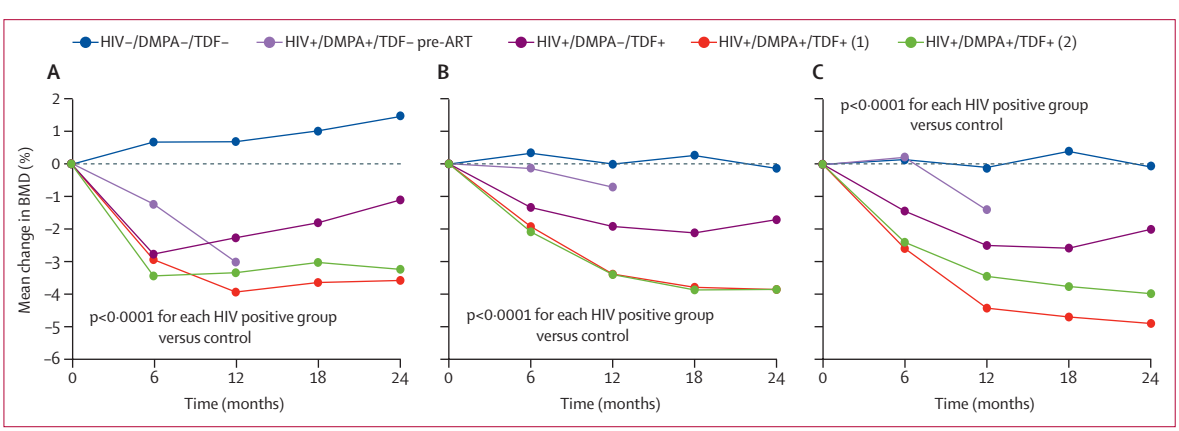

Figure 2: **Mean percent change in BMD among women in the BONE: CARE Study**
Mean percentage change in lumbar spine BMD (A), total hip BMD (B), and femur neck BMD (C). BMD=bone mineral density. DMPA=depot medroxyprogesterone acetate. HIV+/DMPA+/TDF–=HIV positive, DMPA positive, and TDF negative. HIV+/DMPA–/TDF+=HIV positive, DMPA negative, and TDF positive. HIV–/DMPA–/TDF–=HIV negative, DMPA negative, and TDF negative. HIV+/DMPA+/TDF+ (1)=initially HIV positive, DMPA positive, and TDF positive. HIV+/DMPA+/TDF+ (2)=later HIV positive, DMPA positive, and TDF positive. TDF=tenofovir disoproxil fumarate.

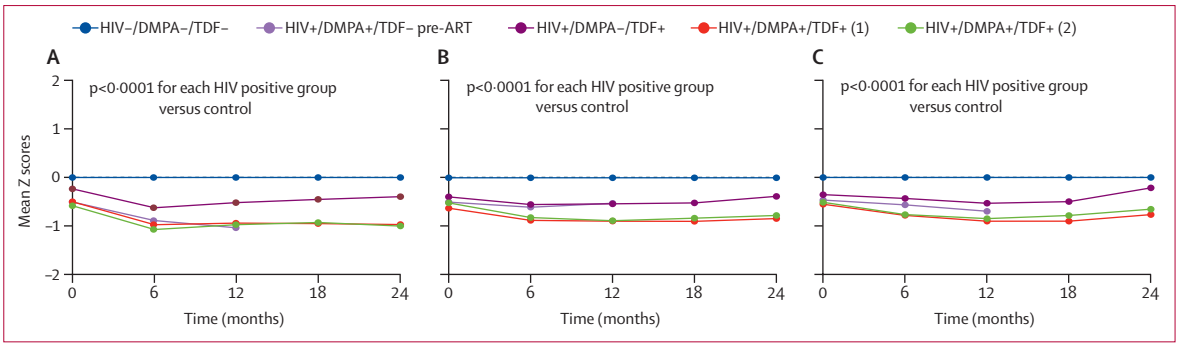

Figure 3: **Mean percent change in BMD Z scores among women in the BONE: CARE Study**
Mean *Z* score for the lumbar spine (A), total hip (B), and femur neck (C). HIV+/DMPA+/TDF+ (1)=initially received HIV positive, DMPA positive, and TDF positive. HIV+/DMPA+/TDF+ (2)=later received HIV positive, DMPA positive, and TDF positive. DMPA=depot medroxyprogesterone acetate. HIV+/DMPA+/TDF–=HIV positive, DMPA positive, and TDF negative. HIV+/DMPA–/TDF+=HIV positive, DMPA negative, and TDF positive. HIV–/DMPA–/TDF–=HIV negative, DMPA negative, and TDF negative. TDF=tenofovir disoproxil fumarate.

ART alone. Similar trends were observed in BMD *Z*-score changes within the different study groups (figure 3). There were no differences in BMD changes among women living with HIV initiating TDF-containing ART with DMPA-IM before (n=159) or under the test-and-treat guidelines (n=166; p=0·16; data not shown). Given that these two groups of DMPA-IM users had the same exposure to TDF and no significant baseline difference in the outcome of interest, BMD (figures 2, 3), we have combined their data for the rest of the results below.

Over the 2-year study period, BMD in the HIV positive, DMPA positive, and TDF positive group declined significantly compared with controls, with a BMD percentage change at the lumbar spine of –4·970% (95% CI –6·391 to –3·549; p<0·0001), –4·151% at the total hip (–5·579, –2·724; p<0·0001), and –4·773% at the femoral neck (–6·424 to –3·122; p<0·0001; table 2). Similarly, there were significant declines in BMD from baseline for the non-hormonal and DMPA-IM users on TDF at all timepoints (table 2, figure 2). Compared with use of TDF alone, concurrent use of DMPA-IM resulted in greater BMD declines over 24 months at all sites, with a decline of –2·677% for the lumbar spine (95% CI –3·743 to –1·611; p<0·0001), –2·518% for the total hip (–3·575 to –1·461; p<0·0001), and –2·907% for the femoral neck (–4·132 to –1·683; p<0·0001), after adjusting for age, BMI, and baseline BMD (p<0·0001 for all; table 2).

The annualised rates of BMD loss were higher in women living with HIV using both DMPA-IM and TDF (HIV positive, DMPA positive, and TDF positive) than women living with HIV on TDF alone (HIV positive, DMPA negative, and TDF positive) or controls (HIV negative, DMPA negative, and TDF negative) at all sites. These changes were significantly different between the three groups after adjusting for baseline BMD, age, and BMI (p<0·001 at all sites; table 3). The annualised rate of bone loss in women living with HIV who were using DMPA-IM was between –1·5% and –2·3% at the different sites and was approximately double that of women living with HIV on TDF alone.

Discussion

We provide the first evidence of the combined deleterious effect of DMPA-IM use and TDF-containing ART initiation on BMD at the hip and lumbar spine in women living with HIV. In a cohort of young adult ART-naive women living with HIV, we found that ART initiation with a TDF-containing regimen was associated with significant declines in BMD, and that concurrent use of DMPA-IM and TDF resulted in a doubling of BMD loss compared with use of TDF alone.

Over the 2-year follow-up period, women living with HIV initiating TDF-containing ART without DMPA-IM had a 2% BMD loss compared with controls whose BMD remained stable. Consistent with these findings, previous studies have demonstrated a 2–6% loss of BMD with ART initiation.[9,21] In a recently published 2-year longitudinal study comparing BMD among black South African women living with HIV, the authors observed that TDF initiation was associated with a loss in BMD of –1·8% at the femoral neck and –2·2% at the total hip that had largely stabilised by 24 months, which are similar to the results we have observed. Our findings suggest that the severity of HIV as measured by decline in CD4 cell count may only play a small role in the process of BMD loss. Baseline analysis did not reveal significant differences in BMD between women living with HIV with CD4 counts lower or higher than 500 cells/μL. This finding suggests that the observed BMD loss in non-hormonal users on TDF was caused by ART and not HIV infection per se. The pathophysiological mechanisms of TDF-related bone loss are not well understood, but may include a direct toxic effect on bone, subclinical tubular dysfunction, and parathyroid hormone-triggered increased bone resorption.[22]

Although our data suggest that the majority of bone loss occurs within 12 months of ART initiation in these young adult women living with HIV, the loss was exaggerated in women living with HIV concurrently using TDF and DMPA-IM. Concurrent use of DMPA-IM and TDF was associated with at least a two-fold increase in BMD loss

	Number	Changes in BMD from baseline (%), g/cm²	p value§	Adjusted difference in BMD (%), g/cm²¶	p value‡	Adjusted difference in BMD (%), g/cm²¶	p value§
Lumbar spine							
Baseline to month 6							
HIV negative, DMPA negative, and TDF negative*	53	0·667 (0·180 to 1·154)	0·0082	Ref	..	..	..
HIV positive, DMPA negative, and TDF positive†	97	−2·772 (−3·258 to −2·285)	<0·0001	−3·302 (−4·228 to −2·376)	<0·0001	Ref	..
HIV positive, DMPA positive, and TDF positive‡	286	−3·201 (−3·551 to −2·850)	<0·0001	−3·972 (−4·793 to −3·150)	<0·0001	−0·673 (−1·339 to −0·006)	0·048
Baseline to month 12							
HIV negative, DMPA negative, and TDF negative*	45	0·682 (−0·040 to 1·403)	0·063	Ref	..	..	..
HIV positive, DMPA negative, and TDF positive†	91	−2·270 (−2·860 to −1·681)	<0·0001	−2·833 (−4·129 to −1·538)	<0·0001	Ref	..
HIV positive, DMPA positive, and TDF positive‡	269	−3·625 (−4·112 to −3·138)	<0·0001	−4·485 (−5·646 to −3·323)	<0·0001	−1·633 (−2·519 to −0·747)	<0·0003
Baseline to month 18							
HIV negative, DMPA negative, and TDF negative*	43	1·001 (0·183 to 1·820)	0·018	Ref	..	..	..
HIV positive, DMPA negative, and TDF positive†	84	−1·811 (−2·540 to −1·082)	<0·0001	−2·521 (−3·992 to −1·049)	0·0008	Ref	..
HIV positive, DMPA positive, and TDF positive‡	254	−3·321 (−3·887 to −2·755)	<0·0001	−4·634 (−5·937 to −3·331)	<0·0001	−2·133 (−3·153 to −1·113)	<0·0001
Baseline to month 24							
HIV negative, DMPA negative, and TDF negative*	38	1·471 (0·584 to 2·359)	0·0018	Ref	..	..	..
HIV positive, DMPA negative, and TDF positive†	83	−1·111 (−1·929 to −0·293)	0·0083	−2·307 (−3·895 to −0·719)	0·0045	Ref	..
HIV positive, DMPA positive, and TDF positive‡	248	−3·406 (−3·969 to −2·844)	<0·0001	−4·970 (−6·391 to −3·549)	<0·0001	−2·677 (−3·743 to −1·611)	<0·0001
Total hip							
Baseline to month 6							
HIV negative, DMPA negative, and TDF negative*	53	0·338 (−0·242 to 0·919)	0·25	Ref	..	..	..
HIV positive, DMPA negative, and TDF positive†	97	−1·341 (−1·790 to −0·891)	<0·0001	−1·568 (−2·488 to −0·647)	0·0009	Ref	..
HIV positive, DMPA positive, and TDF positive‡	286	−2·011 (−2·367 to −1·655)	<0·0001	−2·505 (−3·320 to −1·690)	<0·0001	−0·949 (−1·596 to −0·303)	0·0041
Baseline to month 12							
HIV negative, DMPA negative, and TDF negative*	45	−0·015 (−0·756 to 0·726)	0·97	Ref	..	..	..
HIV positive, DMPA negative, and TDF positive†	91	−1·923 (−2·497 to −1·349)	<0·0001	−2·069 (−3·261 to −0·877)	0·0007	Ref	..
HIV positive, DMPA positive, and TDF positive‡	269	−3·392 (−3·832 to −2·952)	<0·0001	−3·769 (−4·836 to −2·702)	<0·0001	−1·697 (−2·507 to −0·886)	<0·0001
Baseline to month 18							
HIV negative, DMPA negative, and TDF negative*	43	0·261 (−0·658 to 1·179)	0·57	Ref	..	..	..
HIV positive, DMPA negative, and TDF positive†	84	−2·121 (−2·817 to −1·425)	<0·0001	−2·491 (−3·850 to −1·132)	<0·0004	Ref	..
HIV positive, DMPA positive, and TDF positive‡	254	−3·833 (−4·337 to −3·329)	<0·0001	−4·553 (−5·755 to −3·350)	<0·0001	−2·060 (−2·979 to −1·141)	<0·0001
Baseline to month 24							
HIV negative, DMPA negative, and TDF negative*	38	−0·140 (−1·121 to 0·841)	0·77	Ref	..	..	..
HIV positive, DMPA negative, and TDF positive†	83	−1·714 (−2·479 to −0·949)	<0·0001	−1·655 (−3·252 to −0·058)	0·042	Ref	..
HIV positive, DMPA positive, and TDF positive‡	248	−3·856 (−4·449 to −3·264)	<0·0001	−4·151 (−5·579 to −2·724)	<0·0001	−2·518 (−3·575 to −1·461)	<0·0001
Femoral neck							
Baseline to month 6							
HIV negative, DMPA negative, and TDF negative*	53	0·134 (−0·670 to 0·938)	0·74	Ref	..	..	..
HIV positive, DMPA negative, and TDF positive†	97	−1·440 (−2·073 to −0·808)	<0·0001	−1·599 (−2·787 to −0·411)	0·0084	Ref	..
HIV positive, DMPA positive, and TDF positive‡	286	−2·487 (−2·919 to −2·056)	<0·0001	−2·846 (−3·896 to −1·796)	<0·0001	−1·228 (−2·061 to −0·396)	0·0039
Baseline to month 12							
HIV negative, DMPA negative, and TDF negative*	45	−0·125 (−1·112 to 0·862)	0·80	Ref	..	..	..
HIV positive, DMPA negative, and TDF positive†	91	−2·495 (−3·314 to −1·676)	<0·0001	−2·495 (−3·959 to −1·031)	<0·0009	Ref	..
HIV positive, DMPA positive, and TDF positive‡	269	−3·908 (−4·433 to −3·383)	<0·0001	−4·266 (−5·573 to −2·958)	0·0001	−1·748 (−2·738 to −0·758)	0·0006
Baseline to month 18							
HIV negative, DMPA negative, and TDF negative*	43	0·402 (−0·649 to 1·453)	0·44	Ref	..	..	..
HIV positive, DMPA negative, and TDF positive†	84	−2·579 (−3·493 to −1·665)	<0·0001	−2·982 (−4·690 to −1·274)	0·001X	Ref	..
HIV positive, DMPA positive, and TDF positive‡	254	−4·201 (−4·831 to −3·572)	<0·0001	−5·068 (−6·576 to −3·561)	<0·0001	−2·077 (−3·247 to −0·908)	0·0005

(Table 2 continues on next page)

compared with use of TDF alone, even after adjusting for differences in BMI and baseline BMD. We observed similar trends in BMD decline among women living with HIV initiating TDF-containing ART with DMPA-IM at different CD4 cell counts (≤500 cells/μL or >500 cells/μL), further emphasising the importance of TDF-containing ART and DMPA-IM over HIV infection in accounting for bone loss. Because of the hypo-oestrogenic effects of

	Number	Changes in BMD from baseline (%), g/cm²	p value§	Adjusted difference in BMD (%), g/cm²¶	p value‡	Adjusted difference in BMD (%), g/cm²¶	p value§
(Continued from previous page)							
Baseline to month 24							
HIV negative, DMPA negative, and TDF negative*	38	−0·055 (−1·260 to 1·151)	0·93	ref	..	..	..
HIV positive, DMPA negative, and TDF positive†	83	−1·999 (−3·022 to −0·976)	<0·0002	−1·872 (3·725 to −0·018)	0·048	ref	..
HIV positive, DMPA positive, and TDF positive‡	248	−4·422 (−5·078 to −3·766)	<0·0001	−4·773 (−6·424 to −3·122)	<0·0001	−2·907 (−4·132 to −1·683)	<0·0001

Data are % (95% CI). ART=anti-retroviral therapy. BMD=bone mineral density. DMPA=depot medroxyprogesterone acetate. TDF=tenofovir disoproxil fumarate. *Controls (number at baseline 69) were women without HIV using non-hormonal contraception (intra-uterine device or condoms). †Women living with HIV initiating TDF-containing ART without DMPA-IM (number at baseline 106) who were using non-hormonal contraception (IUD or condoms). ‡Women living with HIV initiating TDF-containing ART with DMPA-IM (number at baseline 325) at a CD4 cell count of up to 500 cells/μL combined with those with a cell count of at least 500 cells/μL. §Significant at ≤0·05. ¶Adjusted for age, body-mass index, and baseline BMD. Adjusting for baseline HIV RNA concentrations did not change the inferences.

Table 2: **Adjusted differences in mean BMD percentages at the lumbar spine (L1 to L4), total hip, and femoral neck**

DMPA-IM, current DMPA-IM users without HIV have been shown to have lower mean BMD than non-users and these effects are more pronounced in younger women.[15] Indeed in our baseline analysis, we observed lower BMD among ART-naive current DMPA-IM users compared with previous users and non-users.[18] Similar to the mechanism of TDF-associated BMD loss, studies of bone turnover in DMPA-IM users have suggested that the effects of DMPA-IM on the skeleton are at least partially mediated through increased bone resorption and reduced formation.[23,24] Although we only obtained incomplete data (6 months rather than 2 years) on BMD loss among women living with HIV using DMPA-IM before ART initiation, we demonstrate significant declines in BMD in this group compared with the control group without HIV at the lumbar spine at 24 weeks. This is in contrast to findings from Hileman and colleagues,[25] who reported significant loss in total hip BMD only at 48 weeks. Differences could be caused by small sample sizes, variations in study populations, use of DMPA-IM in our study, or different follow-up periods.

To put our findings into context, during the early menopausal transition in healthy women, the loss of BMD accelerates with annual rates of bone loss between 1·0% and 1·6% per year in the general population.[26] The magnitude of bone loss that we observed with TDF-containing ART initiation alone (0·4–1·1%) approximates that which would be expected during healthy menopause, and with concurrent use of TDF and DMPA-IM (1·8–2·5%) exceeds that seen in late menopause.[26] The 4·6–5·6% cumulative loss in BMD by 24 months among TDF and DMPA-IM users relative to the control group is potentially clinically important. However, whether concurrent use of DMPA-IM and TDF increases fracture risks is unknown. Further studies are needed to establish whether this degree of bone loss is associated with an increased immediate or later risk of fracture, and if the effects of TDF and DMPA-IM on BMD are reversible among women who switch to bone-sparing regimens or stop DMPA-IM use or both.

Our findings are of great public health importance. The high rates of BMD loss possibly result in increased risk of early osteoporosis and fragility fractures in women living with HIV. Worldwide TDF is the most widely prescribed HIV medication; 58% of individuals living with HIV on ART are taking a TDF-containing regimen, and, unless contraindicated, the two preferred first-line ART treatment regimens for adults and children older than 15 years in resouce-limited settings contain TDF.[27] Furthermore, in sub-Saharan African countries with the highest unmet need for contraception, DMPA-IM remains the preferred available contraceptive option across the different age groups with about 38·5% (16·5 million) current users in the sub-Saharan African region alone.[10] The frequently used combination of TDF-containing ART and DMPA-IM exposes millions of individuals living with HIV to its negative effects on bone health.

One of the main strengths of our study is the use of an appropriate comparison group of healthy Ugandan women without HIV, who had not been exposed to hormonal contraception in the previous 2 years, thus

	Percentage annual rate of change (95% CI)*	p value†
Lumbar spine		
HIV negative, DMPA negative, and TDF negative‡	0·707 (0·278 to 1·136)	0·0012
HIV positive, DMPA negative, and TDF positive§	−0·338 (−0·756 to 0·080)	0·11
HIV positive, DMPA positive, and TDF positive¶	−1·532 (−1·820 to −1·244)	<0·0001
Total hip		
HIV negative, DMPA negative, and TDF negative‡	−0·053 (−0·487 to 0·380)	0·81
HIV positive, DMPA negative, and TDF positive§	−0·887 (−1·291 to −0·483)	<0·0001
HIV positive, DMPA positive, and TDF positive¶	−2·025 (−2·315 to −1·735)	<0·0001
Femoral neck		
HIV negative, DMPA negative, and TDF negative‡	0·017 (−0·510 to 0·544)	0·95
HIV positive, DMPA negative, and TDF positive§	−1·111 (−1·621 to −0·600)	<0·0001
HIV positive, DMPA positive, and TDF positive¶	−2·285 (−2·630 to −1·939)	<0·0001

ART=anti-retroviral therapy. BMD=bone mineral density. DMPA-IM=intramuscular depot medroxyprogesterone acetate. TDF=tenofovir disoproxil fumarate. *Adjusted for age, body-mass index, and baseline BMD. †Significant at ≤0·05. ‡Controls (number at baseline 69), who were women without HIV using non-hormonal contraception (intra-uterine device and condoms). §Women living with HIV initiating TDF-containing ART without DMPA-IM (number at baseline 106) who were non-hormonal contraception users (IUD or condoms). ¶Women living with HIV initiating TDF-containing ART with DMPA-IM (number at baseline 325), a group that combine DMPA-IM users who lived with HIV and had a CD4 cell count of up to 500 cells/μL and more than 500 cells/μL.

Table 3: **Mean annualised percentage change in BMD over 24 months**

enabling evaluation of individual effects of the three exposures (HIV positive, DMPA positive, and TDF positive). This control group provides local reference data for healthy young Ugandan women that had previously been unavailable. In addition, the prospective nature of the design with semiannual DXA visits allowed for close assessment of changes in BMD over time. Two potential sources of error, temporal sequence and recall bias, were also minimised by the prospective design and the relatively short intervals between follow-up visits allowing participants to accurately recall their details about ART adherence and contraceptive use. Furthermore, to ensure that participants were adherent to their contraception and ART, contraceptive services and viral-load testing were offered as part of the study. These elements could have been responsible for the high rates of virological suppression and consistent contraceptive use attained in this study. Lastly, our sample size of 521 women including 452 women living with HIV, and high retention overall (81%) provides more than 90% power to detect significant differences for our analyses. In fact, this large sample size provided flexibility to do separate per-protocol analyses for women with optimal exposure to both TDF and DMPA-IM. We showed greater bone loss among participants who consistently used DMPA-IM and were virally suppressed, a finding that further strengthens our conclusions.

The study has some limitations, including absence of randomisation of the women living with HIV to the different contraceptive methods. However, bias related to differences between women who choose DMPA-IM versus non-hormonal contraception was minimised by collecting data on exposures known to affect BMD in young women. First, during analysis, careful assessment of potential confounders and construction of multivariable models were central to our evaluation of the associations between the change in BMD and ART initiation with a TDF-containing regimen, with or without DMPA-IM. We also used a random-effects model that takes into account intra-individual correlations when estimating annualised rates of BMD loss. Second, we did not present comprehensive data on the contribution of DMPA-IM alone to BMD loss among untreated women living with HIV because of a change in the treatment guidelines during study implementation, nor do we include complementary data on trabecular-bone score assessments, markers of subclinical injury (eg, retinol-binding protein and β-2 and α-1 microglobulin), parathyroid hormone, 25 hydroxyvitamin D, and bone turnover biomarkers that are important mediators in bone metabolism[22] that would further support more detailed conclusions about the underlying mechanisms of the observed associations. In addition, we are not able to quantify fracture risk in this study population because we did not do vertebral fracture assessments. Lastly, our study was comprised of only Ugandan women, which might limit the generalisability of our findings. However, the results are more likely to generalise to other populations in sub-Saharan Africa than studies done on other continents.

In summary, this longitudinal analysis provides evidence of additional BMD loss among women living with HIV with a doubling of loss among women on TDF-containing ART who were concurrently using DMPA-IM for contraception compared with those on non-hormonal contraception. Identification and use of safer contraceptive and ART options for women living with HIV is a high priority. Given strong preference for injectable contraceptives in sub-Saharan Africa, additional research on the effects of other available alternative injectable options, such as norethisterone enanthate (Noristerat; Bayer, Berlin, Germany) given bimonthly, on BMD in women living with HIV is recommended. Before establishing an injectable bone-sparing contraceptive, women need more clear counselling messages on the risks associated with the relative short-term use of DMPA-IM. Furthermore, newer bone-sparing ART might have a promising role in delivering the vision of sustained undetectable viral load, while minimising comorbid risks.[28,29] Our ongoing phase-IV clinical trial, the BONE: STAR study[30] that is assessing the effect of switching from TDF to tenofovir alafenamide-containing ART on bone mass and turnover among DMPA-IM users over a 2-year period provides a timely opportunity to obtain comprehensive safety data on tenofovir alafenamide-containing ART in the context of hormonal (DMPA-IM) and non-hormonal contraceptive use before tenofovir alafenamide roll-out in resource-limited settings.

Contributors

FKM contributed to the conceptualisation, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualisation, and writing of the original draft. TTB, MGF, JMP, MEB, and DS contributed to the conceptualisation, funding acquisition, methodology, validation, visualisation, and writing, review, editing of this manuscript. JMP further contributed to investigation. NK and MN contributed to data curation, formal analysis, validation, visualisation, and writing, review, editing of this manuscript. All authors approved the final manuscript.

Declaration of interests

TTB has received consulting fees from Merck, ViiV Heathcare, Gilead Sciences, Janssen, and Theratecnologies. FKM has received money to her institution from Gilead Sciences. All other authors declare no competing interests.

Data sharing

Data can be shared with qualifying researchers who submit a proposal with a valuable research question as assessed by the BONE: CARE protocol team. A contract should be signed. Requests should be directed to fmatovu@mujhu.org or fmatovu@musph.ac.ug.

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