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Switch from tenofovir disoproxil fumarate combination to dolutegravir with rilpivirine improves parameters of bone health

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Objective: Bone mineral density (BMD) loss, a risk factor for osteoporosis, has been attributed to HIV infection and antiretroviral therapy (ART), including regimens containing tenofovir disoproxil fumarate.

Design: Study 202094 is an open-label, parallel-group, sub-study of the phase III SWORD-1 and SWORD-2 studies (ClinicalTrials.gov identifier, NCT02478632).

Methods: HIV-1-infected adults with HIV-1 RNA less than 50 copies/ml who received ART containing tenofovir disoproxil fumarate for at least 6 months were randomized to receive dolutegravir with rilpivirine or continue current ART regimen. Total hip and lumbar spine BMD were measured by dual-energy X-ray absorptiometry (DXA) scans. The primary endpoint was percentage change from baseline in total hip BMD.

Results: DXA scans were evaluable for 81 participants at baseline and Week 48. Percentage increase in total hip BMD was significantly greater in participants who switched to dolutegravir with rilpivirine (1.34%) compared with participants who continued current ART (0.05%; treatment difference, +1.29%; 95% CI 0.27–2.31; $P = 0.014$). Lumbar spine BMD significantly increased in the dolutegravir with rilpivirine group by 1.46% (95% CI 0.65–2.28) compared with 0.15% (95% CI −0.79 to 1.09) in the current ART group (treatment difference, 1.32; 95% CI 0.07–2.57; $P = 0.039$). Participants in the dolutegravir with rilpivirine group experienced significantly greater reductions in bone formation and resorption biomarkers compared with the current ART group.

Conclusion: Switch to dolutegravir with rilpivirine was associated with significant improvement in BMD and bone turnover markers compared with tenofovir-based three-drug regimens, providing a robust option for preserving bone health while continuing suppressive ART.

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Keywords: bone mineral density, dual-energy X-ray absorptiometry, FRAX, lumbar spine, nucleoside reverse transcriptase inhibitor-sparing, total hip, two-drug regimen

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Introduction

Bone disease is an important comorbidity in the aging HIV population [1–3]. Numerous studies have shown that patients with HIV experience a decline in bone mineral density (BMD) and higher bone fracture incidence compared with the general population [4]. A meta-analysis of cross-sectional studies reported pooled odds ratios of 6.4 for reduced BMD and 3.7 for osteoporosis in HIV-infected compared with non-HIV-infected patients [5]. In addition, a large study that evaluated data in a United States healthcare system revealed overall fracture prevalence of 2.87% in HIV-infected patients compared with 1.77% in non-HIV-infected patients [5]. Loss of BMD in patients with HIV is associated with many contributing factors including antiretroviral therapy (ART), particularly regimens including tenofovir disoproxil fumarate [5,6]. Mechanisms that may cause ART-associated BMD loss remain uncertain but may include mitochondrial toxicity, urinary phosphate wasting, and renal osteodystrophy [7]. Reports have described improved BMD after switching from regimens containing tenofovir disoproxil fumarate to regimens containing other nucleoside reverse transcriptase inhibitors (NRTIs) [8,9].

Two-drug regimens (2DRs) are being developed to simplify HIV treatment by using combinations of agents that retain virologic efficacy comparable with that of three-drug regimens but limit toxicity risks [10]. A retrospective observational cohort study showed preliminary support for the efficacy and safety of a regimen constituting the integrase strand transfer inhibitor (INSTI) dolutegravir and the non-NRTI (NNRTI) rilpivirine [11]. Both dolutegravir and rilpivirine have demonstrated high potency for inhibition of HIV-1 in phase III studies [11–17]. The virologic potency and pharmacologic attributes of dolutegravir and rilpivirine led to their selection for development as a 2DR to maintain suppression of HIV-1 [18,19].

In the SWORD-1 and SWORD-2 trials, participants with HIV who were virologically suppressed for at least 6 months were randomized to continue with their current ART regimen or switch to the 2DR of dolutegravir with rilpivirine. This report describes a sub-study (202094) of SWORD-1 and SWORD-2 to evaluate changes at Week 48 in BMD and bone turnover biomarkers after switching from a three-drug regimen containing tenofovir disoproxil fumarate to the NRTI-sparing dolutegravir with rilpivirine regimen.

Methods

Study design and participants

Study 202094 (ClinicalTrials.gov identifier, NCT 02478632) is an open-label, parallel-group sub-study of two identical phase III clinical studies, SWORD-1 and SWORD-2 (ClinicalTrials.gov identifiers, NCT 02429791 and NCT02422797, respectively). These parent studies were global, multicentre, randomized (1 : 1), open-label, parallel-group, noninferiority studies of adults with HIV-1 infection with HIV-1 RNA suppressed to less than 50 copies/ml while receiving ART. SWORD study participants were randomized to switch to dolutegravir with rilpivirine or remain on current ART through Week 48. The first participant was screened for the sub-study on 12 June 2015, and the data cutoff for the 48-week analysis was 22 November 2016. Thirty-two investigational centres in six countries (Argentina, 4; Belgium, 3; Canada, 4; Spain, 12; United Kingdom, 2; United States, 7) participated. Participants in SWORD-1 or SWORD-2 who were receiving a stable ART regimen containing tenofovir disoproxil fumarate were eligible for the sub-study. Key exclusion criteria included less than three vertebra in the L1–L4 range suitable for BMD measurement; bilateral hip replacement; uncontrolled thyroid disease; male hypogonadism; endocrine diseases; fragility fracture history; severe osteoporosis [indicated by prior dual-energy X-ray absorptiometry (DXA) scan-derived *T* score of −3.5 or lower]; BMI less than 18 kg/m^2 or at least 40 kg/m^2; 25-hydroxy vitamin D less than 15 ng/mm^3 (37.5 $nmol/mm^3$) and current use of or intent to initiate tamoxifen, bone-related treatment, or anabolic steroids (except for testosterone if received at a stable dose for the last 6 months before entry and with no plan to discontinue during the study); and treatment with or intent to initiate anticonvulsant therapy or other hormonal therapy, unless given for at least 6 months before study entry with no plan to discontinue during the study.

All participants gave written informed consent before the sub-study commenced. This study was conducted under approval from national, regional, or investigational site ethics committees in accordance with the 2008 Declaration of Helsinki.

Randomization and masking

As part of the SWORD parent studies, participants were randomized [1 : 1, RAMOS NG (GlaxoSmithKline, Research Triangle Park, North Carolina, USA)] to receive open-label dolutegravir 50 mg with rilpivirine 25 mg once daily or continue with current ART through Week 48. Randomization was stratified by baseline third-agent class (INSTI, NNRTI, or protease inhibitor), age group (< 50 years or ≥ 50 years), and planned participation in the sub-study.

Procedures and assessments

The primary endpoint was percentage change from baseline to Week 48 in total hip BMD (as areal density in g/cm^2), which includes femoral neck, trochanter, and intertrochanter areas. The key secondary endpoint was percentage change from baseline to Week 48 in lumbar spine (L1–L4) BMD (as areal density in g/cm^2).

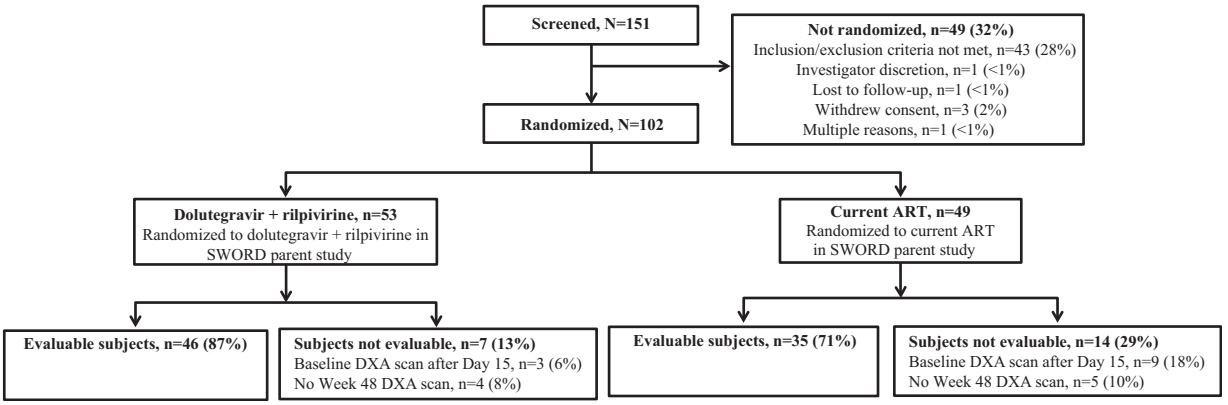

Fig. 1. Disposition of participants. ART, antiretroviral therapy; DXA, dual-energy X-ray absorptiometry.

Additional secondary endpoints were change from baseline to Week 48 in total hip and lumbar spine BMD assessed as *T* scores and *Z* scores and total hip and lumbar spine BMD assessed as areal density, *T* scores, and *Z* scores by baseline third-agent class (INSTI, NNRTI, protease inhibitor). Exploratory endpoints included change from baseline to Week 48 in fracture risk [as measured by FRAX (University of Sheffield, Sheffield, United Kingdom) score [20]] and bone turnover biomarkers (i.e. type 1 collagen cross-linked C-telopeptide, bone-specific alkaline phosphatase, procollagen type 1 *N*-propeptide, osteocalcin). This substudy only assessed adverse events related to the DXA scan procedure.

DXA scans were performed using non-DOS-based GE Lunar or Hologic scanners on Day 1 (baseline) and at Week 48 or at the withdrawal visit and read centrally by the DXA vendor (PAREXEL International, Durham, North Carolina, USA); the vendor was blinded to the treatment arm of study participants. Within-site longitudinal and cross-site calibration data generated at sites by phantom scans were reviewed and applied by the DXA vendor before reporting BMD as areal density (g/cm^2), *T* scores, or *Z* scores. Image acquisition guidelines for total hip and lumbar spine DXA scans were provided to all study sites by the DXA vendor, with study-specific training including review of the requirement for strict adherence to these guidelines provided by local study monitors at all sites. Biomarkers were assessed during study visits at Day 1 and Week 48 or withdrawal in all substudy participants. Bone marker analysis was performed with cryopreserved blood samples by a central laboratory (Q^2 Solutions, Valencia, California, USA) using standardized assays as follows: type 1 collagen cross-linked C-telopeptide was quantified by an enzyme-linked immunoassay; bone-specific alkaline phosphatase was quantified by an immunoenzymatic assay; procollagen type 1 *N*-propeptide was quantified by radioimmunoassay; and osteocalcin was quantified by electrochemiluminescence assay.

Statistical analysis

The primary objective was to evaluate the percentage change from baseline to Week 48 in total hip BMD (g/cm^2) in the dolutegravir with rilpivirine group compared with the current ART group. Target study enrolment was at least 100 patients, with a goal of ~150 patients. Assuming a true population effect of a 1.9% treatment difference with a SD of 3.5%, a sample size of 100 participants provided 77% power for demonstrating a statistically significant result.

The sub-study population included all participants who were registered in the sub-study and received at least one dose of dolutegravir with rilpivirine or current ART. Data analyses were based on the intent-to-treat-exposed DXA population and used all evaluable participants. Participants were considered evaluable if they had DXA scan results available at both baseline and Week 48. An analysis of covariance model, adjusted for baseline BMD, baseline BMI, and age, was used to test for differences between treatment arms in percentage change from baseline at Week 48 in total hip and lumbar spine BMD. The same model was used to analyse *T* and *Z* scores, adjusting for baseline *T* or *Z* score accordingly instead of baseline BMD. An analysis of covariance model with log-transformed bone biomarker data was used to analyse change from baseline in bone turnover biomarkers, adjusting for baseline third-agent class, age, sex, BMI, smoking status, and baseline bone turnover biomarker value. All data formatting, tabulations, and calculations were performed using SAS software version 9.1.3 or higher (SAS Institute, Inc, Cary, North Carolina, USA).

Results

Study population

Of 151 participants screened, 49 participants were excluded on the basis of inclusion/exclusion criteria ($n = 43$), investigator discretion ($n = 1$), lost to follow-up ($n = 1$), withdrew consent ($n = 3$), or multiple reasons

Table 1. Summary of baseline characteristics.

	Dolutegravir with rilpivirine ($n=53$[a])	Current ART ($n=49$[a])
Age, median (min, max), years	43.0 (21, 62)	46.0 (22, 76)
≥50 years, *n* (%)	15 (28)	16 (33)
Women, *n* (%)	27 (51)	26 (53)
White race, *n* (%)	44 (83)	40 (82)
BMI at baseline, mean (SD) [min, max], kg/m^2	25.2 (3.9) [18.7, 33.3]	25.8 (4.8) [18.9, 38.7]
Baseline CD4$^+$ lymphocyte count, *n* (%), cells/μl		
≥500	31 (58)	33 (67)
Baseline third-agent class, *n* (%)		
NNRTI	32 (60)	33 (67)
INSTI	9 (17)	5 (10)
Protease inhibitor	12 (23)	11 (22)
History of smoking at baseline, *n* (%)		
Never/not current smoker	40 (75)	36 (73)
<1 pack-year[b]	10 (19)	8 (16)
≥1 pack-year[b]	3 (6)	5 (10)
Alcohol consumption at baseline, *n* (%)		
No alcohol consumption	37 (70)	30 (61)
<14 units per week[c]	15 (28)	17 (35)
≥14 units per week[c]	1 (2)	2 (4)
Baseline BMD, mean (SD), g/cm^2		
Total hip	$n=50$	$n=40$
	0.964 (0.1457)	0.974 (0.1146)
Lumbar spine	$n=52$	$n=42$
	1.063 (0.1613)	1.086 (0.1495)
Total hip *T* score, *n* (%)	$n=50$	$n=40$
Normal (>−1)	36 (72)	32 (80)
Osteopenia (−2.5 to ≤−1)	14 (28)	8 (20)
Osteoporosis (≤−2.5)	0	0
Lumbar spine *T* score, *n* (%)	$n=52$	$n=42$
Normal (>−1)	29 (56)	26 (62)
Osteopenia (−2.5 to ≤−1)	20 (38)	14 (33)
Osteoporosis (≤−2.5)	3 (6)	2 (5)

ART, antiretroviral therapy; BMD, bone mineral density; INSTI, integrase strand transfer inhibitor; max, maximum; min, minimum; NNRTI, non-nucleoside reverse transcriptase inhibitor.
[a]Unless otherwise noted.
[b]A pack-year is defined as 20 cigarettes (a pack) smoked every day for a year.
[c]A unit of alcohol is 1 half-pint of beer, 1 glass of wine, or 1 short measure of spirits.

($n=1$); 102 participants were included in the sub-study (Fig. 1). Twenty-one participants did not have evaluable DXA scans at baseline and at Week 48. Twelve of these participants (dolutegravir with rilpivirine, three; current ART, nine) did not have a baseline DXA scan after Day 15, eight participants (dolutegravir with rilpivirine, four; current ART, four) were withdrawn from the parent study before providing a DXA scan at Week 48, and one participant (current ART) incorrectly switched to dolutegravir with rilpivirine on the day of the Week 48 scan; hence, the scan was excluded from the analysis. Therefore, 81 participants (dolutegravir with rilpivirine, $n=46$; current ART, $n=35$) had evaluable DXA scans at baseline and Week 48. Among the 12 participants with no evaluable DXA scan at baseline, one current ART participant withdrew after completing the Week 48 DXA scan. Nine participants withdrew in total (dolutegravir with rilpivirine, four; current ART, five). Participant demographics at baseline, including age, ethnicity, sex, BMD, and BMI, were balanced between the two groups (Table 1). Approximately half of the participants in both treatment groups were women, the majority of study participants were nonsmokers and did not consume alcohol, and baseline third-agent classes were mostly NNRTI-based without significant differences between treatment arms. Most study participants in both treatment arms had normal total hip and lumbar spine *T* scores. Less than 30% were classified as osteopenic, and no participants met the osteoporosis criterion by total hip *T* score. However, slightly greater than 30% were osteopenic in both treatment arms, and approximately 6% met the osteoporosis criterion by lumbar spine *T* score (Table 1).

Changes in bone mineral density

The percentage increase in total hip BMD measured by areal density from baseline to Week 48 was significantly greater in participants who switched to dolutegravir with rilpivirine (1.34%) compared with current ART (0.05%; difference in adjusted percentage change, +1.29%; 95% CI 0.27–2.31; $P=0.014$; Fig. 2). The percentage increase in lumbar spine BMD from baseline to Week 48 (1.46%) was also significantly greater in the dolutegravir with rilpivirine group compared with the current ART group (0.15%; difference in adjusted percentage change, 1.32; 95% CI 0.07–2.57; $P=0.039$; Fig. 2). The significant total hip result was also supported by a significant difference between

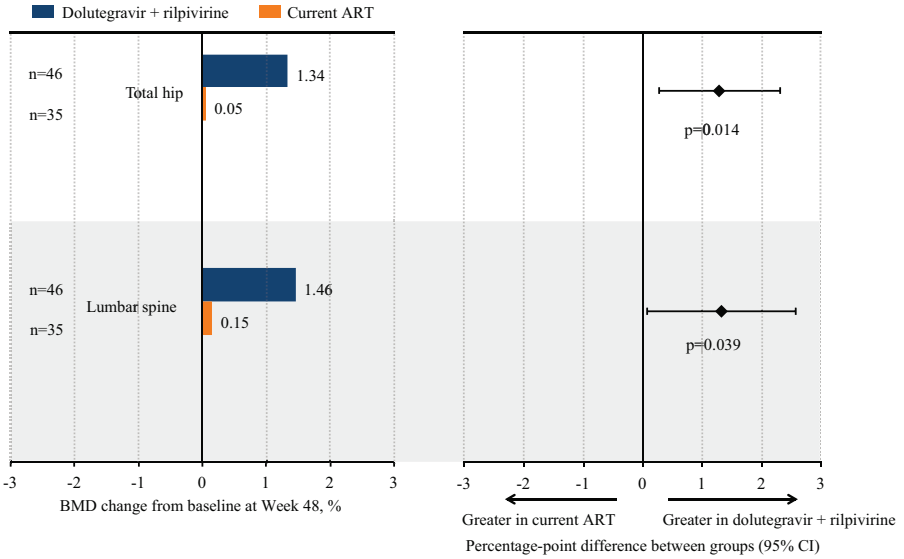

Fig. 2. Change from baseline in total hip and lumbar spine bone mineral density at Week 48. ART, antiretroviral therapy; BMD, bone mineral density; CI, confidence interval.

treatment arms in the adjusted change from baseline to Week 48 in the total hip *T* score (difference in adjusted percentage change: 0.09; 95% CI 0.02–0.16; $P = 0.016$). A similar observation was made for the mean difference in adjusted change from baseline to Week 48 in the lumbar spine *T* score (difference in adjusted percentage change: 0.12; 95% CI 0.00–0.23; $P = 0.049$). A significantly greater increase from baseline to Week 48 was also observed in total hip and lumbar spine *Z* scores for the dolutegravir with rilpivirine group compared with the current ART group ($P = 0.026$ and $P = 0.013$, respectively).

The change from baseline to Week 48 in total hip and lumbar spine BMD, expressed as areal density, was evaluated across demographic subgroups (age and sex) and baseline BMI. These results supported the primary analysis because a greater change from baseline was observed in the dolutegravir with rilpivirine group compared with the current ART group across all demographic subgroups; however, statistical comparisons were limited by the small sample size within each category (Fig. 3). Demographic groups at greater risk for BMD loss (e.g. ≥50 years of age, women, and BMI $<25\,kg/m^2$) exhibited greater increases in adjusted percentage change from baseline to Week 48 in total hip BMD in the dolutegravir with rilpivirine group compared with the current ART group (Fig. 3). Additionally, greater increases in point estimates of mean adjusted change from baseline in total hip and lumbar spine BMD were observed in participants in the dolutegravir with rilpivirine group compared with the current ART group regardless of baseline third-agent class (INSTI, NNRTI, or protease inhibitor; Fig. 3). Differences between groups within each baseline third-agent class were not significant, but this may be attributed to the small sample size within each class.

There was little change from baseline to Week 48 for participants in the dolutegravir with rilpivirine or current ART groups in the 10-year probability of hip fracture (−0.08 and 0.03%, respectively) and osteoporotic fracture (−0.12 and −0.04%, respectively) as assessed by FRAX score [20].

A post hoc analysis from baseline to Week 48 showed that participants in the dolutegravir with rilpivirine group had a similar mean change in BMI ($0.84\,kg/m^2$) compared with the current ART group ($0.62\,kg/m^2$). Vitamin D supplementation was reported for 20 of the 102 participants at baseline and did not change markedly through Week 48, with discontinuation of vitamin D reported for three participants (dolutegravir with rilpivirine, two; current ART, one).

Changes in bone biomarkers

Participants in the dolutegravir with rilpivirine group experienced significantly greater reductions from baseline to Week 48 in bone-specific alkaline phosphatase, osteocalcin, procollagen type 1 *N*-propeptide, and type 1 collagen cross-linked C-telopeptide compared with the current ART group (*P* value range from <0.001 to 0.029 across markers; Table 2). These results were consistent with those for concentrations of the same bone turnover biomarkers following analysis of pooled data from the SWORD-1 and SWORD-2 studies ($N = 991$) [21].

Safety

No adverse events were attributable to the DXA scan procedure. Clinically significant loss of BMD (defined as ≥5%) at Week 48 was reported in one 31-year-old male participant (dolutegravir with rilpivirine group). This participant's BMI was $21.8\,kg/m^2$ at baseline and dropped

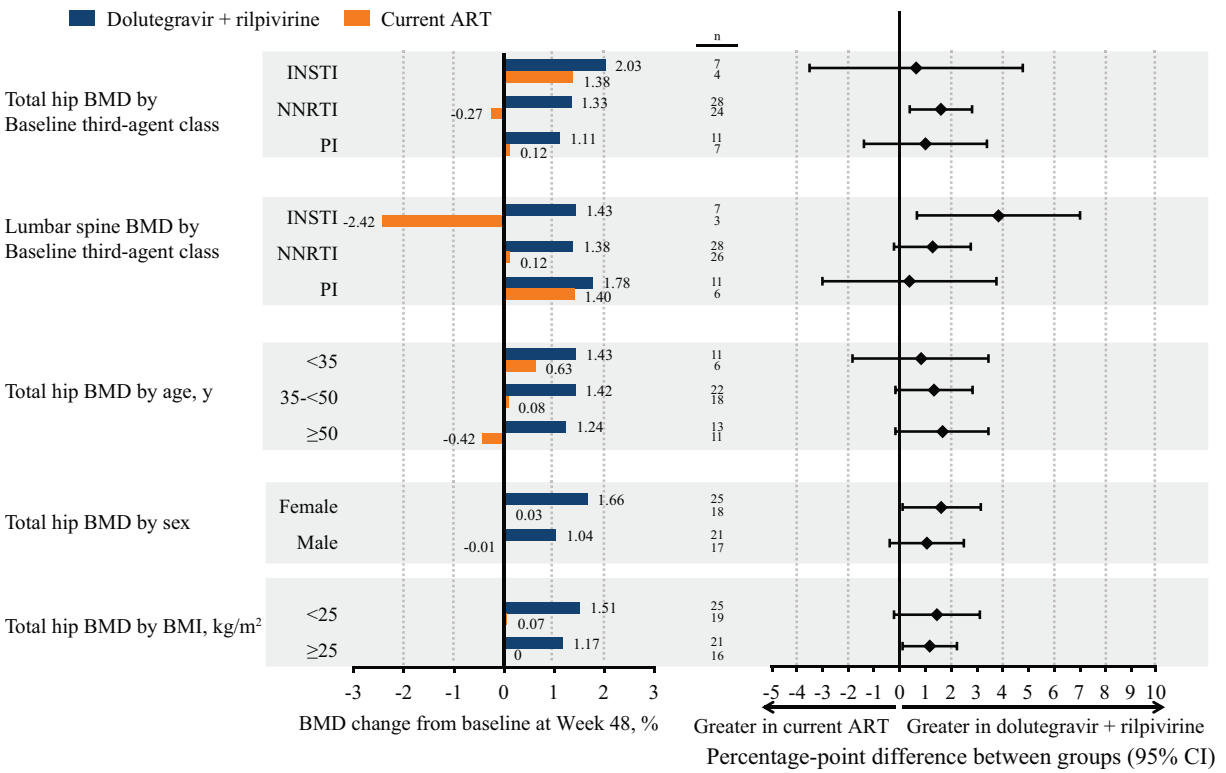

Fig. 3. Comparison of change in bone mineral density from baseline to 48 weeks by subgroup. ART, antiretroviral therapy; BMD, bone mineral density; CI, confidence interval; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

to 20.5 kg/m^2 at Week 48. The participant was a current smoker, had vitamin D levels within the normal range, and did not receive vitamin D or calcium supplementation during the study period. The investigator concluded that pharmacological intervention was not required. One 61-year-old postmenopausal female participant experienced a nontraumatic fracture of the right fibula (current ART group). This was considered an adverse event of moderate intensity but was not related to study treatment. This participant's BMI remained stable in the normal range during the study period; her vitamin D level was 80 nmol/mm^3 at baseline, and the level had decreased to 50 nmol/mm^3 at Week 48. However, she was osteopenic at baseline, with a T score of −2.01 which further decreased to −2.33 at Week 48.

Discussion

The primary analysis of the 202094 sub-study of the pooled SWORD-1 and SWORD-2 study populations demonstrated that participants who received dolutegravir with rilpivirine had an increase from baseline to Week 48 in total hip (1.34%) and lumbar spine BMD (1.46%), which differed significantly ($P = 0.014$ and $P = 0.039$, respectively) from participants who continued to receive ART containing tenofovir disoproxil fumarate. We selected total hip BMD as the primary measurement of interest because hip is composed of more compact cortical bone and less trabecular bone compared with lumbar spine [22]; therefore, change in total hip BMD is the more conservative endpoint because it changes less readily in comparison with lumbar spine BMD. The significant changes in total hip BMD demonstrated a marked positive effect on bone health after switching from tenofovir disoproxil fumarate-containing three-drug regimens to the NRTI-sparing 2DR, dolutegravir with rilpivirine.

Although a limited number of switch studies that replaced tenofovir disoproxil fumarate with other NRTIs like abacavir or tenofovir alafenamide showed a beneficial effect on BMD [8,23], this is the first randomized study to show that a switch from a tenofovir disoproxil fumarate-based regimen to an NRTI-sparing regimen led to a beneficial effect on BMD and bone turnover markers. A small study ($n = 37$) replaced tenofovir disoproxil fumarate with raltegravir, but this was a nonrandomized study, and many participants remained on an NRTI, often emtricitabine [9].

Data for other secondary endpoints, including evaluation of change in BMD expressed as T and Z scores and evaluation of change in BMD over 48 weeks by baseline third-agent class, supported the primary endpoint

Table 2. Change from baseline in bone turnover markers at Week 48.

	Week 48 to baseline ratio (95% CI)				
	Dolutegravir with rilpivirine ($n=53$)	Current ART ($n=49$)	Treatment ratio[b] (95% CI)	*P* value	*P* value interaction term[c]
Bone biomarker[a]					
Bone-specific alkaline phosphatase	0.753 (0.704–0.805); $n=48$	1.145 (1.068–1.227); $n=45$	0.658 (0.595–0.726)	<0.001	0.233
Procollagen type 1 *N*-propeptide	0.660 (0.612–0.712); $n=49$	0.891 (0.823–0.966); $n=44$	0.740 (0.661–0.828)	<0.001	0.314
Type-1 collagen cross-linked C-telopeptide	0.669 (0.590–0.758); $n=49$	0.837 (0.734–0.954); $n=45$	0.800 (0.664–0.963)	0.019	0.118
Osteocalcin (by baseline third-agent class)					
INSTI	0.635 (0.537–0.751); $n=8$	1.059 (0.848–1.323); $n=5$	0.600 (0.456–0.789)	0.003	NA[d]
NNRTI	0.787 (0.721–0.859); $n=29$	0.932 (0.852–1.020); $n=29$	0.845 (0.744–0.958)	0.029	NA[d]
Protease inhibitor	0.682 (0.588–0.790); $n=12$	1.011 (0.871–1.172); $n=11$	0.675 (0.550–0.827)	0.002	NA[d]

ART, antiretroviral therapy; CI, confidence interval; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.
[a]Bone biomarkers are analysed based on log-transformed data. Estimates were initially calculated from an analysis of covariance model adjusting for baseline third-agent class, age, sex, BMI category, smoking status, and baseline biomarker level.
[b]Treatment ratio is the ratio of Week 48 to baseline ratios between treatment arms.
[c]*P* value for interaction between treatment groups. If the interaction between third agent and treatment was significant at a 10% significance level, then the results were presented by third agent. This level of interaction was observed for the osteocalcin data set.
[d]Not applicable to individual classes; *P* value for interaction between treatment group and baseline third-agent class was 0.083.

analysis. Despite the limited number of participants in some subgroup categories, data from subgroup analyses were consistent with and supportive of the primary endpoint analysis. The beneficial effect seems consistent in high-risk populations such as older participants, women, and smokers.

In a post hoc analysis, participants in the dolutegravir with rilpivirine and current ART groups had similar mean BMI values at baseline. We observed small but similar changes from baseline in BMI in both groups at Week 48. As there was no significant treatment effect on BMI at Week 48, the effect of dolutegravir with rilpivirine on total hip BMD at Week 48 is unlikely to be confounded by concurrent changes in BMI.

In addition to the consistent effect on BMD, we observed significant decreases in bone turnover markers after the switch. Bone undergoes constant remodelling, with osteoclasts resorbing older bone and osteoblasts laying down new bone, and the actions of osteoclasts and osteoblasts can be assessed *in vivo* using bone turnover markers [5]. These processes are normally tightly coupled, but in HIV, especially whenever initiating tenofovir disoproxil fumarate-containing ART, accelerated bone resorption results in net bone loss. In our study, among participants receiving dolutegravir with rilpivirine, the decreases from baseline to Week 48 in levels of bone formation markers (bone-specific alkaline phosphatase, procollagen type 1 *N*-propeptide, and osteocalcin) and the bone resorption marker type-1 collagen cross-linked C-telopeptide were significantly greater than the decreases in all bone turnover biomarkers in participants who continued current ART. Taken together, these data indicate a lower rate of bone turnover in participants who received dolutegravir with rilpivirine compared with those who continued current ART.

This sub-study did not demonstrate any significant effect of dolutegravir with rilpivirine on FRAX scores. This was not surprising because many of the 12 input parameters (e.g. age, BMI, alcohol intake, smoking status, medical history) needed to calculate FRAX scores did not change in this relatively short 48-week study.

The protocol attempted to limit the effect of factors that affect bone density by permitting only stable testosterone or female hormone replacement therapy given for at least 6 months before baseline with no intention to stop during the study; excluding participants with male hypogonadism, uncontrolled thyroid disease, vitamin D deficiency, or severe osteoporosis at baseline; and prohibiting osteoporosis medications (e.g. bisphosphonates). These eligibility criteria prohibited recruitment of some SWORD study participants to the sub-study. We acknowledge the limitations of this bone sub-study. Enrolment of 102 participants provided adequate statistical power for the comparison of change in total hip BMD (as areal density) but not for all categories in the various subgroup analyses. Further, the sub-study was limited by the use of only one time point after baseline (Week 48). Additional assessments may have provided a more detailed analysis of the treatment differences. However, both parent studies and this sub-study are ongoing, with subsequent analyses at weeks 100 and 148 after all participants have been switched to dolutegravir with rilpivirine. Participants in the parent studies randomized to current ART at baseline switched to

dolutegravir with rilpivirine at Week 52 if virologically suppressed at Week 48.

No adverse events were considered attributable to the DXA scan procedure; however, there were treatment-related adverse events reported in the parent SWORD-1 and SWORD-2 studies [21]. Over 70% of participants in each treatment group reported adverse events (dolutegravir with rilpivirine, 77%; current ART, 71%); however, adverse events leading to withdrawal were low for both treatment groups (dolutegravir with rilpivirine, 3%; current ART, <1%), indicating that the regimens were well tolerated. Other studies involving switches to regimens containing rilpivirine (GS-US-366–1160 [24] and SPIRIT [25]) or dolutegravir (STRIIVING [26]) have also reported that patients in the current ART groups experienced fewer overall adverse events or discontinuations because of adverse events compared with the switch groups. However, there may be an inherent bias toward the current ART group in switch studies because of the number of years of experience participants had with the previous regimen (GS-US-366–1160, not reported; SPIRIT, 2.8 years; STRIIVING, >4 years; SWORD-1 and SWORD-2, ~4 years). In these trials, patients in the current ART groups experienced fewer adverse events compared with the switch groups (GS-US-366–1160, 74 versus 80%; SPIRIT, only reported percentages for grades 3 and 4 adverse events; STRIIVING, 47 versus 66%; SWORD-1 and SWORD-2, 71 versus 77%; respectively) and fewer discontinuations because of adverse events (GS-US-366–1160, 2 versus 3%; SPIRIT, 0 versus <1%; STRIIVING, 0 versus 4%; SWORD-1 and SWORD-2, < 1 versus 3%; respectively). Overall, discontinuations because of adverse events were low in the switch groups, which is consistent with increases in treatment satisfaction in the switch group compared with the current ART group in both the STRIIVING and SWORD-1 and SWORD-2 trials.

The little change observed in hip and lumbar spine BMD in participants in the current ART group was expected because the detrimental effect of certain ART regimens on BMD has been reported to slightly decrease [24,27] and stabilize after 1 or 2 years [4]. Participants in the current ART group were receiving tenofovir-containing regimens for at least 6 months before randomization and then another 48 weeks before being switched to dolutegravir with rilpivirine. The observed changes from baseline to Week 48 in total hip and lumbar spine BMD (expressed as areal density, *T* scores, and *Z* scores), together with the reduction in bone turnover markers, provide evidence that the switch from a three-drug or four-drug ART regimen containing tenofovir disoproxil fumarate to dolutegravir with rilpivirine was associated with bone health maintenance at minimum, and possibly an improvement through 48 weeks. Together, the BMD and bone marker data from the sub-study indicate that switching to the NRTI-sparing 2DR, dolutegravir with rilpivirine, limits the deleterious effect of ART on BMD and improves markers of bone health, while maintaining viral suppression in patients living with HIV-1 infection.

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Conflicts of interest

G.M. has served as a consultant for Gilead and Merck. S.L., D.P., and M.C.P. have nothing to disclose. J.D. has served on advisory boards for ViiV Healthcare, Gilead, and Merck; has been a speaker for ViiV Healthcare and Merck; and has been a part-time consultant for Gilead Marketing and AbbVie Canada. L.K., B.W., M.G., and M.A. are employees of ViiV Healthcare and GlaxoSmithKline shareholders. K.A. and M.C. are employees and shareholders of GlaxoSmithKline. K.V. is an employee of Janssen.

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