Less Bone Loss With Maraviroc- Versus Tenofovir-Containing Antiretroviral Therapy in the AIDS Clinical Trials Group A5303 Study

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Background. There is a need to prevent or minimize bone loss associated with antiretroviral treatment (ART) initiation. We compared maraviroc (MVC)- to tenofovir disoproxil fumarate (TDF)–containing ART.

Methods. This was a double-blind, placebo-controlled trial. ART-naive subjects with human immunodeficiency virus type 1 RNA load (viral load [VL]) >1000 copies/mL and R5 tropism were randomized to MVC 150 mg or TDF 300 mg once daily (1:1), stratified by VL <100 000 or ≥100 000 copies/mL and age <30 or ≥30 years. All subjects received darunavir 800 mg, ritonavir 100 mg, and emtricitabine 200 mg daily. Dual-energy X-ray absorptiometry scanning was done at baseline and week 48. The primary endpoint was percentage change in total hip bone mineral density (BMD) from baseline to week 48 in the as-treated population.

Results. We enrolled 262 subjects. A total of 259 subjects (130 MVC, 129 TDF) contributed to the analyses (91% male; median age, 33 years; 45% white, 30% black, 22% Hispanic). Baseline median VL was 4.5 $\log_{10}$ copies/mL and CD4 count was 390 cells/μL. The decline in hip BMD (n = 115 for MVC, n = 109 for TDF) at week 48 was less with MVC (median [Q1, Q3] of −1.51% [−2.93%, −0.11%] vs −2.40% [−4.30%, −1.32%] for TDF ($P < .001$). Lumbar spine BMD decline was also less with MVC (median −0.88% vs −2.35%; $P < .001$). Similar proportions of subjects in both arms achieved VL ≤50 copies/mL in as-treated and ITT analyses.

Conclusions. MVC was associated with less bone loss at the hip and lumbar spine compared with TDF. MVC may be an option to attenuate ART-associated bone loss.

Clinical Trials Registration. NCT01400412.

Keywords. maraviroc; tenofovir; bone; darunavir.

Bone mineral density (BMD) declines by 2%–6% in the 2 years following antiretroviral therapy (ART) initiation, and the magnitude depends in part on the ART regimen [1–5]. Use of tenofovir disoproxil fumarate (TDF) has been linked to a 1%–2% greater bone loss than other nucleos(t)ide reverse transcriptase inhibitors (NRTIs) [3, 5–8]. The bone loss after ART initiation is greatest within the first 24–48 weeks [5, 9, 10], suggesting that it may be linked to systemic immunologic and inflammatory changes that are also pronounced in the initial weeks to months after ART initiation [11, 12].

Maraviroc (MVC) has virologic activity against R5-tropic human immunodeficiency virus type 1 (HIV-1) through inhibition of CC chemokine receptor 5 (CCR5), the main coreceptor for HIV-1 [13]. Studies

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of potential immunomodulatory and antiinflammatory effects of MVC have produced conflicting results [14–18]. CCR5 is expressed on both osteoblasts and osteoclasts, and one of CCR5's primary ligands is macrophage inflammatory protein 1 alpha (MIP-1α), which has been shown to increase osteoclastogenesis and inhibit osteoblast function in preclinical models [19–21]. CCR5 may play an important role in the signaling between osteoblasts and osteoclasts [19]. Thus, it is plausible that MVC would have a beneficial effect on bone mineralization in the context of ART initiation.

The AIDS Clinical Trials Group (ACTG) study A5303 was conducted to investigate the effects of MVC on bone loss after ART initiation in treatment-naive HIV-1–infected patients. Our a priori hypothesis was that initiating a MVC-containing ART regimen would be associated with less bone loss compared to a regimen containing TDF. We also compared the antiretroviral efficacy of the regimens.

METHODS

Study Design

A5303 was a phase 2, prospective, double-blind, placebo-controlled, multicenter, 48-week clinical trial conducted at 33 ACTG and 4 Adolescent Trials Network research sites in the United States. Eligible subjects were ART-naive patients (aged ≥18 years) with plasma HIV-1 RNA concentration (viral load [VL]) >1000 copies/mL and R5 tropism by Trofile phenotypic assay (Monogram Biosciences, South San Francisco, California). The inclusion and exclusion criteria are listed at ClinicalTrials.gov (NCT01400412). The institutional review board of each study site approved the protocol. Each participant provided written informed consent.

Study Procedures

Eligible subjects were randomized (1:1) to MVC 150 mg plus TDF placebo or TDF 300 mg plus MVC placebo, stratified by screening VL <100 000 or ≥100 000 copies/mL and age <30 or ≥30 years. Each subject also received darunavir 800 mg, ritonavir 100 mg, and emtricitabine 200 mg. Although the recommended dose of MVC is 150 mg twice daily when combined with ritonavir-boosted darunavir (DRV/r) [22], we selected a dose of 150 mg once daily based on pharmacokinetic and clinical studies supporting this lower dosing [23–27]. Subjects were instructed to take the study drugs with food once daily.

Within 4 weeks prior to randomization, each subject underwent a baseline dual-energy X-ray absorptiometry (DXA) scan of the left hip and lumbar spine (L1–L4) at the study site, using either a Lunar (GE Healthcare, Fairfield, Connecticut) or Hologic (Hologic Incorporated, Bedford, Massachusetts) DXA scanner. A second DXA scan was performed at week 48 (±4 weeks) using the same DXA scanning system. For subjects who had a permanent change in the MVC or TDF component of their randomized regimen or who prematurely discontinued the study, DXA scanning was performed at the time of discontinuation. All DXA scans were read centrally at the Body Composition Analysis Center at Tufts University. The European Spine Phantom was used for cross-calibration of DXA machines and quality assurance at each site. The *z* scores—the number of standard deviations a subject's BMD falls from the mean BMD—were calculated from the site-specific BMD measures using normative data matched for age, sex, and race. The *z* scores were chosen over *t* scores given the relatively young age of the study population [28].

Routine study visits after randomization occurred at week 4 (±7 days), and weeks 16, 24, 36, and 48 (all ±14 days). Viral load (Abbott Real*Time* assay HIV-1, lower detection limit of 40 copies/mL), CD4 cell count, hematology, liver function tests, and blood chemistry were measured at each visit. Adherence to study medications was assessed by self-report at all study visits postentry except week 36.

Study Endpoints

The primary endpoint was the percentage of change in total hip BMD from baseline to week 48. The main secondary endpoint was the percentage of change in lumbar spine BMD from baseline to week 48. Other secondary endpoints included time to virologic failure, proportion of subjects with VL <50 copies/mL, changes in CD4 cell count from baseline, emergent resistance during failure, and incidence plus severity of adverse events. Virologic failure was defined as 2 consecutive VL results >1000 copies/mL at or after week 16 and before week 24, or >200 copies/mL at or after week 24. A confirmatory VL measurement was obtained within 30 days of receiving an initial virologic failure result. Subjects who discontinued the study with an unconfirmed virologic failure result were considered to have virologic failure at the visit week of the initial result. Time to virologic failure was defined as the time from study entry to the visit week of the initial failure; subjects without evidence of virologic failure had their time to virologic failure censored at the study week of their last VL measurement. Emergent resistance was assessed using plasma samples obtained at the virologic failure confirmation visit by genotyping the HIV-1 reverse transcriptase and protease genes.

Statistical Analyses

The target sample size of 127 subjects per arm (total of 254) provided 90% power to detect a difference of 1.5% or larger in total hip BMD change from baseline to week 48 between the 2 arms, assuming that 20% of subjects would be nonevaluable due to scan failure or loss to follow-up. This sample size also provided 87% power to claim noninferiority of the MVC arm for the virologic efficacy aim, assuming a cumulative probability of virologic failure of 15% in both arms by week 48, a maximum allowable difference of 15%, and 10% loss to follow-up.

The primary analysis was as-treated and included only subjects who remained on their randomized treatment without any interruption of >10 weeks. Intent-to-treat (ITT) analyses that included outcomes regardless of status on randomized treatment were also performed using 3 different approaches to handle missing BMD data. The first approach assumed that missing data occurred completely at random, and thus only included subjects with total hip BMD measurements available at both baseline and week 48 (complete case). The other approaches used to handle missing data assumed informative missing data. Specifically, missing week 48 measurements were imputed with (1) the last available DXA scan measurement while on randomized regimen after at least 12 weeks of study treatment (last observation carried forward), and (2) an arbitrary value less than any percentage week 48 change from baseline, that is, largest decrease from baseline (worst rank). Stratified Wilcoxon rank-sum tests were used to test for differences between the 2 treatment groups, stratified by age (<30 vs ≥30 years). Wilcoxon signed-rank tests were used to test for within-treatment-group changes greater than zero; 95% confidence intervals (CIs) for

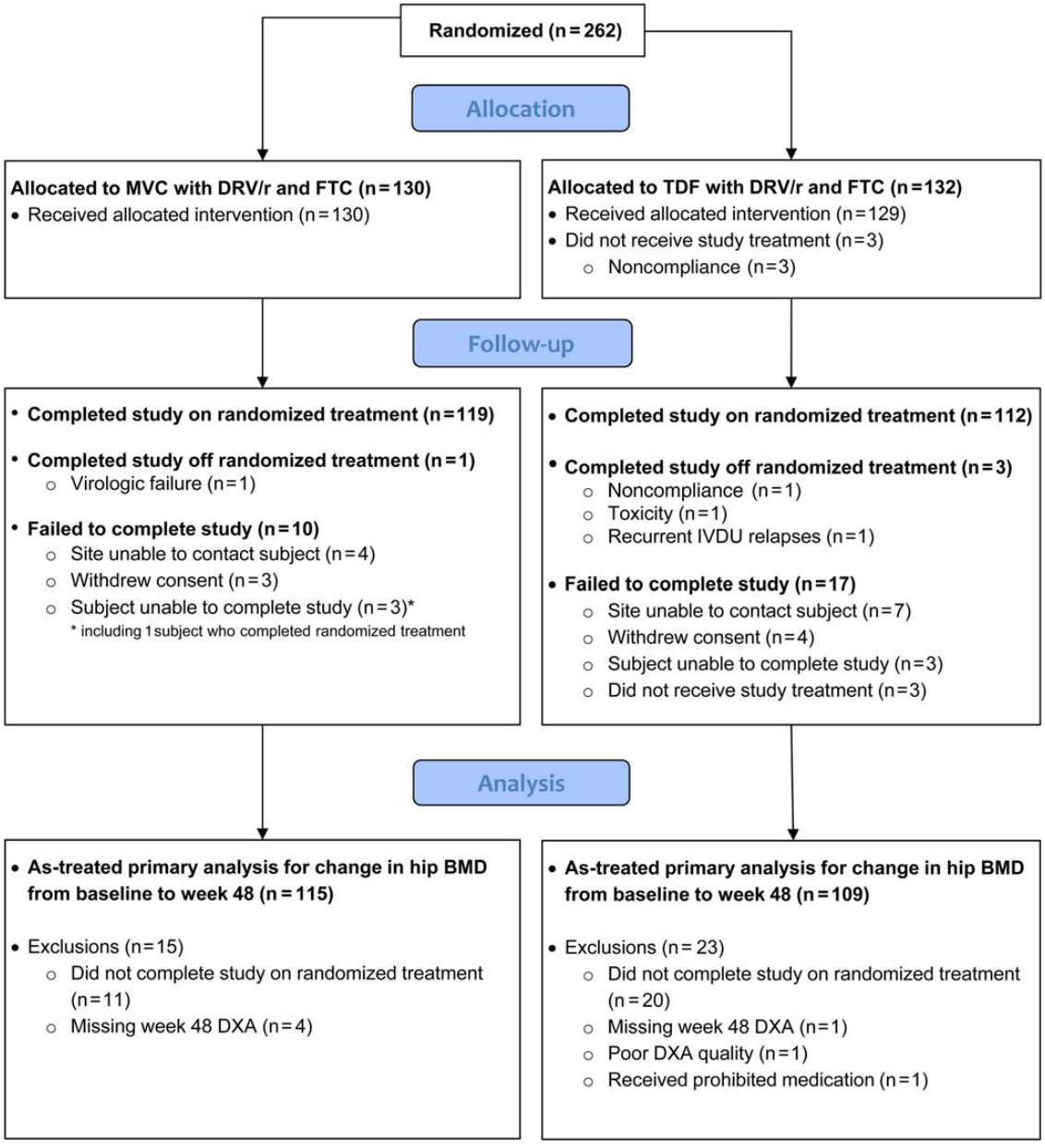

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. Abbreviations: BMD, bone mineral density; DRV/r, darunavir/ritonavir; DXA, dual-energy X-ray absorptiometry; FTC, emtricitabine; IVDU, intravenous drug user; MVC, maraviroc; TDF, tenofovir disoproxil fumarate.

median changes within treatment group were estimated using distribution-free method via percentiles. Linear regression models were used to evaluate interactions between treatment arm and age, baseline VL, and race/ethnicity (post hoc).

Product-limit estimates were used to estimate the cumulative probability of virologic failure over time and its corresponding 95% CI for each treatment group. The difference in these estimated probabilities at week 48 was estimated with a 95% CI stratified by VL at screening; stratum specific variances on the estimated 48-week failure probability were used to define the stratum weights and compared (upper bound) against the noninferiority boundary of 15 percentage points. The proportion of subjects in each arm with VL ≤50 copies/mL at weeks 24 and 48 was calculated using the as-treated approach described above as well as 2 ITT analyses (missing VL ignored; missing VL equals failure [>50 copies/mL]).

Analyses of CD4 count used the same as-treated population as the BMD as-treated analysis. Safety analyses included all subjects who started study treatment. All statistical tests were 2-sided and interpreted at the 5% nominal level of significance without adjustment for multiple comparisons. Analyses were conducted using SAS statistical software version 9.4.

RESULTS

Figure 1 shows the disposition of the 262 subjects enrolled in the trial. Three subjects (all from the TDF arm) never initiated study treatment and were excluded from all analyses. The analyzed population (N = 259 [130 MVC, 129 TDF]) was 91% male, with a median age of 33 years; 45% non-Hispanic white (white), 30% non-Hispanic black (black), and 22% Hispanic. At baseline, median VL was 4.5 $\log_{10}$ copies/mL, and CD4 count was 390 cells/μL. Baseline demographics and disease characteristics were generally similar between the study arms, but there was a chance imbalance with more black subjects and more

Table 1. Baseline Characteristics and Bone Mineral Density

Characteristic	MVC (n = 130)	TDF (n = 129)	Total (N = 259)
Age, y			
Median (Q1, Q3)	33 (26, 42)	33 (26, 42)	33 (26, 42)
<30 y	49 (38)	48 (37)	97 (37)
≥30 y	81 (62)	81 (63)	162 (63)
Sex			
Male	115 (88)	120 (93)	235 (91)
Female	15 (12)	9 (7)	24 (9)
Race/ethnicity			
White non-Hispanic	57 (44)	59 (46)	116 (45)
Black non-Hispanic	45 (35)	33 (26)	78 (30)
Hispanic	24 (18)	34 (26)	58 (22)
Other	4 (4)	3 (3)	7 (2)
HIV-1 RNA, $\log_{10}$ copies/mL, median (Q1, Q3)	4.59 (3.91, 5.07)	4.47 (4.02, 4.91)	4.50 (3.97, 5.00)
HIV-1 RNA, copies/mL			
<100 000	92 (71)	102 (80)	194 (75)
≥100 000	38 (29)	26 (21)	64 (25)
CD4 count, cells/μL, median (Q1, Q3)	389 (295, 496)	392 (290, 518)	390 (294, 517)
Hepatitis C antibody positive	10 (8)	12 (9)	22 (8)
Creatinine clearance, mL/min			
Median (Q1, Q3)	124 (105, 152)	126 (106, 139)	124 (106, 145)
>90 mL/min	90%	89%	90%
Body mass index, kg/m^2, median (Q1, Q3)	25 (22, 29)	26 (23, 29)	25 (23, 29)
BMD, median (Q1, Q3)			
Total hip BMD, g/cm^2	1.05 (0.96, 1.18)	1.03 (0.95, 1.15)	1.04 (0.95, 1.17)
z score	−0.2 (−0.9, 0.6)	−0.1 (−0.8, 0.6)	−0.1 (−0.8, 0.6)
Lumbar spine BMD, g/cm^2	1.16 (1.03, 1.28)	1.11 (1.00, 1.20)	1.14 (1.02, 1.25)
z score	−0.2 (−1.0, 0.6)	−0.3 (−1.3, 0.6)	−0.3 (−1.1, 0.6)
Femoral neck BMD, g/cm^2	1.01 (0.88, 1.13)	0.94 (0.85, 1.07)	0.98 (0.86, 1.12)
z score	0.0 (−0.8, 0.8)	−0.2 (−0.9, 0.6)	−0.1 (−0.8, 0.7)

Data are presented as No. (%) unless otherwise specified.

Abbreviations: BMD, bone mineral density; HIV-1, human immunodeficiency virus type 1; MVC, maraviroc; TDF, tenofovir disoproxil fumarate.

subjects with baseline VL >100 000 copies/mL in the MVC arm (Table 1). Subjects in both study arms had similar baseline BMD.

BMD Changes

The primary as-treated analysis of the percentage of change from baseline to week 48 in hip BMD included 224 subjects (115 subjects in the MVC group and 109 in the TDF group). As shown in Figure 2*A*, there was a decline in hip BMD in both arms, which was smaller in the MVC group ($P < .001$): the median (Q1, Q3) percentage of change in BMD was −1.51% (−2.93%, −0.11%) for the MVC group compared with −2.40% (−4.30%, −1.32%) for the TDF group. Lumbar spine BMD also declined less in the MVC group than in the TDF group ($P = .001$); median (Q1, Q3) percentage of change was −0.88% (−2.93%, 1.30%) for the MVC group and −2.35% (−4.25%, −0.45%) for the TDF group. ITT analyses yielded similar conclusions (all $P < .001$; data not shown).

Given the chance racial and VL imbalance at randomization, a post hoc linear regression analysis adjusting for race (black vs other) was performed. Following initial model diagnostics, 2 outlying data points were excluded. Analyses were adjusted for age and baseline VL as well as baseline BMD at the relevant body site. Although adjustment for age stratum, baseline VL, and race/ethnicity did not alter the primary finding of a smaller decline in hip BMD in the MVC group compared with TDF ($P \leq .001$), a differential effect of MVC by race/ethnicity was apparent (interaction between study treatment and race/ethnicity; $P = .034$, Figure 3). This interaction appears to have been driven by a smaller decline in BMD with MVC among black participants (Figure 2). The estimated difference between MVC vs TDF in percentage of bone loss in hip over 48 weeks among nonblack participants was 0.71% (95% CI, −0.13% to 1.55%; $P = .096$), compared with 2.34% (95% CI, 1.10%–3.58%; $P = .0003$) in black participants. The observed difference in BMD loss at the spine between the MVC and TDF groups was larger in black participants compared with nonblack participants; however, this difference was not statistically significant ($P = .31$). The estimated difference between MVC vs TDF in percentage of spine BMD loss over 48 weeks in nonblack participants was 1.15% (95% CI, .13%–2.18%; $P = .028$) compared with 2.09% (95% CI, .58%–3.61%; $P = .007$) in black participants. No evidence of treatment interactions with age or baseline VL was apparent at either the hip or spine ($P > .59$).

Efficacy and Safety

There were 14 virologic failures (8 in the MVC group and 6 in the TDF group) by week 48, 10 of which were confirmed (8 in the MVC group and 2 in the TDF group) and 4 (all in the TDF arm) who were lost to follow-up after initial failure. The median difference between the arms (MVC minus TDF) in the

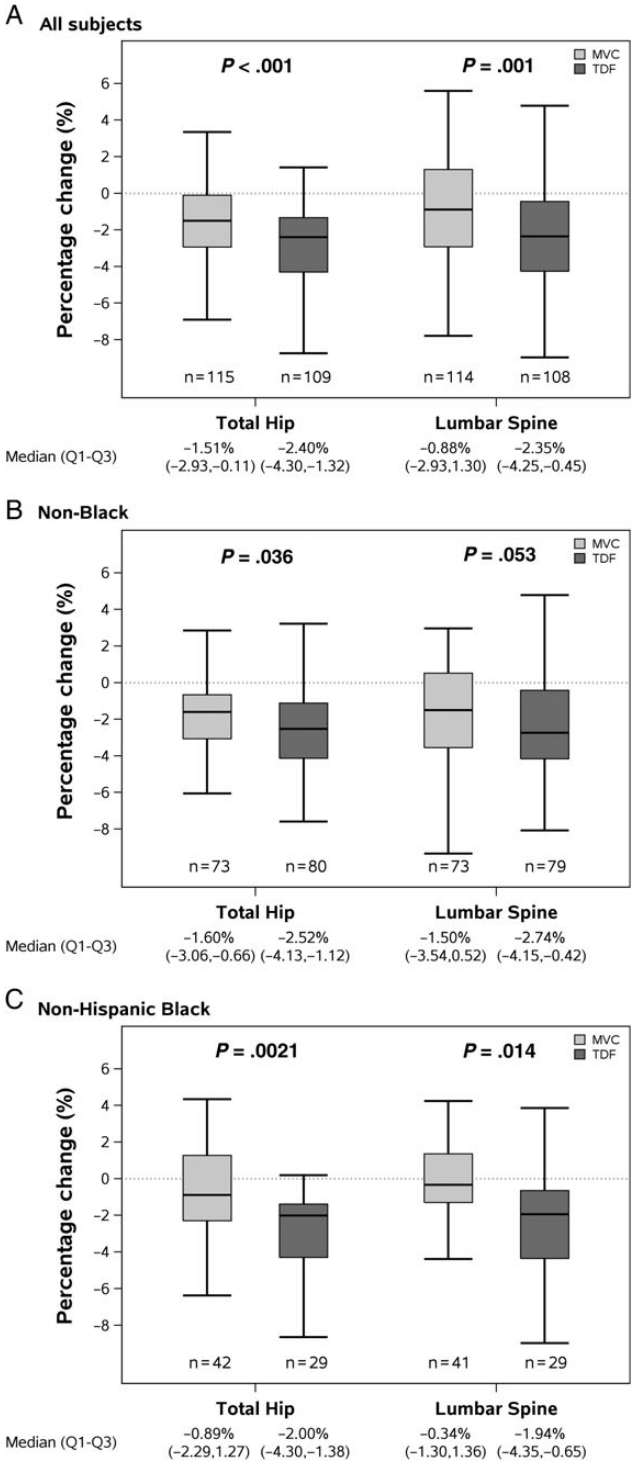

Figure 2. Percentage of change in bone mineral density from baseline to week 48 among all participants (*A*), nonblack participants (*B*), and non-Hispanic black participants (*C*). The line inside the box indicates the median value. The lower and upper edges of the box indicate the first and third quartiles (the 25th and 75th percentiles). The lower and upper whiskers are the first and third quintiles ±1.5 times interquartile range. Stratified Wilcoxon rank-sum tests were used to test for differences between the 2 treatment groups, stratified by age (<30 vs ≥30 years). Abbreviations: MVC, maraviroc; TDF, tenofovir disoproxil fumarate.

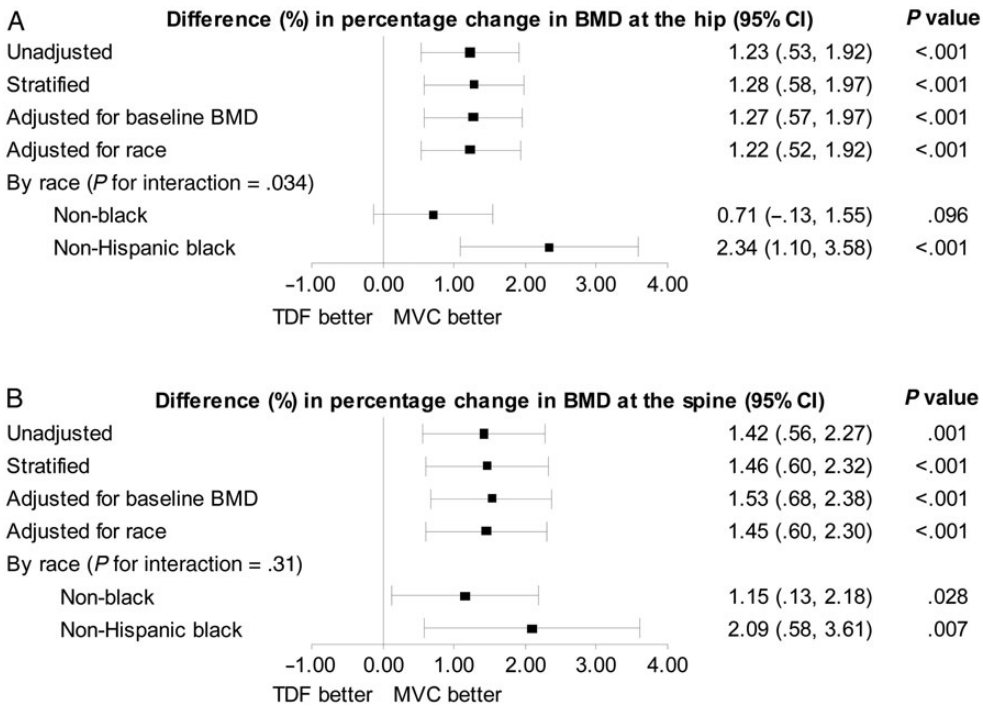

Figure 3. Adjusted treatment effects on the percentage of change in hip (*A*) and spine (*B*) bone mineral density (BMD) from baseline to week 48 with 95% confidence intervals (CIs). Following initial model diagnostics, 2 extreme outlying and influential data points were excluded: an extreme decrease (−32.1%) in the maraviroc (MVC) group and extreme increase (+26.6%) in the tenofovir disoproxil fumarate (TDF) group. Estimates from simple linear regression analyses are (1) unadjusted, (2) stratified by age (<30 y, ≥30 y) and baseline human immunodeficiency virus type 1 (HIV-1) RNA (<100 000, ≥100 000 copies/mL), (3) adjusted for baseline BMD at the specific site, (4) adjusted for race (nonblack vs non-Hispanic black), and (5) adjusted by race. Models 3–5 are also stratified by age and baseline HIV-1 RNA level; models 4 and 5 also adjust for baseline BMD.

cumulative probability of virologic failure while on randomized treatment (as-treated) was 2% (95% CI, −4% to 5%), which was well within the predefined noninferiority margin (Table 2). In as-treated analysis, VL ≤50 copies/mL was achieved in 85% and 93% of subjects in the MVC and TDF arms, respectively, at week 24 ($P = .061$), whereas 94% had VL ≤50 copies/mL in both arms at week 48 ($P = .893$). ITT analyses yielded similar results (Table 2). Four subjects (3 in the MVC group and 1 in the TDF group) underwent successful genotyping, of whom 1 subject (on MVC) had the M184V NRTI mutation and the polymorphic mixture V118I/V. There were no protease inhibitor (PI) resistance-associated mutations.

Significant within-group increases in CD4 count occurred from baseline to week 48 in both groups ($P < .001$). The median (Q1, Q3) increase in the MVC group was 234 (131, 327) cells/μL, which was greater than the increase of 188 (94, 304) cells/μL in the TDF group ($P = .036$). Both regimens were well tolerated. Grade 3 adverse events occurred in 10% of subjects in the MVC arm and 14% of those on TDF, whereas 2% and 3%, respectively, experienced grade 4 adverse events (Supplementary Table 1). There were no deaths.

DISCUSSION

We determined BMD changes in HIV-1–infected patients initiating MVC vs TDF, each combined with DRV/r and emtricitabine. Similar to other studies [1–5], BMD declined over the first 48 weeks in both treatment groups. However, the magnitude of the decline was less in the MVC arm, with a median of −1.5% at the hip and −0.9% at the lumbar spine, compared with −2.4% and −2.4%, respectively, in the TDF arm. These results are consistent with randomized trials of TDF- vs abacavir-containing regimens that found approximately 1%–2% greater BMD decline with TDF use [3, 5, 7, 8]. The results also recapitulate the findings of a recent clinical trial of TDF vs tenofovir alafenamide (TAF), an oral tenofovir prodrug that achieves high intracellular levels of the active metabolite, tenofovir diphosphate, while maintaining 90% lower plasma levels of tenofovir than TDF. At week 48, TAF combined with elvitegravir-cobicistat resulted in −0.7% BMD loss at the hip and −1.3% decline at the lumbar spine compared with −3.0% and −2.9%, respectively, with TDF [29].

Post hoc analysis motivated by a chance racial imbalance at randomization revealed that the difference in BMD loss with

Table 2. Cumulative Probability of Virologic Failure and Proportion With Human Immunodeficiency Virus Type 1 RNA ≤50 Copies/mL

Treatment Group	Study Week	(As-Treated) Cumulative Probability of Virologic Failure, % (95% CI)[a]	Proportion With HIV-1 RNA ≤50 copies/mL, %		
			On-Treatment	ITT, Missing Date Ignored	ITT, Missing Equals Failure
MVC					
	16	0 (0–0)			
	24	4 (2–9)	85	85	83
	36	5 (2–10)			
	48	5 (2–10)	94	93	86
TDF					
	16	1 (0–5)			
	24	2 (1–7)	93	93	87
	36	2 (1–7)			
	48	3 (1–9)	94	92	81
			95% CI for between-arm difference (MVC-TDF) at 24 wk		
			(–16%, 0%)	(–16%, 0%)	(–13%, 5%)
Between-arm difference (MVC-TDF) by 48 wk[b]			95% CI for between-arm difference (MVC-TDF) at 48 wk		
		2 (–4, 5)	(–6%, 7%)	(–6%, 8%)	(–4%, 15%)

Abbreviations: CI, confidence interval; HIV-1, human immunodeficiency virus type 1; ITT, intent-to-treat; MVC, maraviroc; TDF, tenofovir disoproxil fumarate.

[a] Product limit estimate of the cumulative probability of virologic failure while on randomized treatment. Subjects without prior virologic failure are censored at the earliest of discontinuation of randomized treatment or end of study.

[b] Stratified by screening HIV-1 RNA stratum.

MVC compared to TDF was greater in black participants compared with other racial/ethnic groups, reaching statistical significance at the hip but not the lumbar spine. This observation appears to have been driven by less BMD loss with MVC among black subjects.

Nonuse of TDF is the putative explanation for the lower BMD decline in the MVC arm of our study. The mechanisms of TDF's negative impact on BMD remain uncertain, but may include direct effects of tenofovir on bone cells, or indirect effects on calcium-phosphate homeostasis, resulting in inadequate bone mineralization [30, 31]. It is less clear whether MVC had a protective effect, although the interaction between BMD changes in the MVC arm and race is intriguing. Race was not evaluated in a small (N = 27) 48-week study that showed a 2.1% increase in proximal femur BMD after switching from virally suppressive triple ART to MVC 300 mg plus DRV/r [32]. The divergence of MVC's effect in racial/ethnic groups is unlikely to be explained by any of the theoretical pathways for a beneficial bone effect of MVC. One proposed pathway is that MVC may modulate factors that contribute to skeletal deterioration such as proinflammatory and immunomodulatory cytokines [33–35]. The evidence on whether MVC attenuates systemic immune activation and inflammation independent of its virologic effects, however, remains mixed [14–16]. Another hypothetical pathway for a beneficial skeletal effect of MVC involves the proosteoclastogenic MIP-1α, a CCR5 ligand [19–21]. Because bone is continuously remodeled by bone-forming osteoblasts and bone-resorbing osteoclasts, inhibition of MIP-1α may tip the balance toward bone formation. Further examination of the effects of MVC on biomarkers of inflammation and immune activation and the associations with BMD changes and race/ethnicity is planned.

MVC was combined with emtricitabine and DRV/r in our study. Emtricitabine has not been independently implicated in bone loss, although its bone effects have not been previously investigated to our knowledge. In contrast, use of some ritonavir-boosted PIs has been associated with more bone loss in multiple studies [3, 8, 36, 37]. In the randomized trial of 3 initial regimens containing TDF and emtricitabine (A5260s), for example, BMD loss at 96 weeks was comparable between DRV/r and atazanavir/ritonavir recipients, whereas both of these groups experienced a greater decline than the raltegravir group [37]. Whereas the greater bone loss with boosted PIs has been attributed to higher tenofovir levels when TDF and boosted PIs are coadministered [38], the relationship between boosted PIs and bone health is more complex and has not been fully elucidated. In A5224s, independent effects of atazanavir/ritonavir vs efavirenz were seen in the lumbar spine but not the hip, and the effect of TDF on bone did not differ between the atazanavir/ritonavir and efavirenz arms [3]. In vitro studies have shown evidence of PI effects on osteoblast and osteoclast function, as well as inhibition of 1-α hydroxylase activity, which converts 25-hydroxyvitamin D to bioactive 1,25-dihydroxyvitamin D [39–41]. Studies of MVC-containing regimens that do not

include boosted PIs and tenofovir may further illuminate the interactions between MVC and bone loss.

An unapproved MVC dose of 150 mg daily was used in this study. This dosing was based on several studies [23–27], and is affirmed by our finding of similar virologic efficacy between the experimental MVC regimen and the TDF-containing standard of care. Of note, the MODERN (Maraviroc Once-Daily with Darunavir Enhanced by Ritonavir in a New Regimen) study was terminated prematurely due to inferiority of MVC 150 mg plus DRV/r 800/100 mg once daily vs the same TDF-containing comparator used in our study [42]. Addition of emtricitabine to MVC 150 mg plus DRV/r 800/100 mg in our study likely contributed to the regimen's impressive efficacy. It is unknown whether conventional MVC dosing would amplify any beneficial effect of MVC or uncover untoward effects. Another limitation of our study is the dearth of information on the clinical significance of observed differences in BMD decline between MVC vs TDF. However, cumulative TDF exposure has been independently associated with osteoporotic fracture [36]. We did not evaluate the impact of smoking and alcohol use as these data were not collected prospectively. Finally, the participants were relatively young (median age, 33 years) and only 9% were female, limiting the study's generalizability.

Taken together, our findings demonstrate BMD differences that may be expected with MVC- vs TDF-based initial ART.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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