Less Bone Loss with a Maraviroc Regimen in HIV-infected Treatment-Naïve Subjects

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ABSTRACT

Background: Bone mineral density (BMD) decreases by 2-6% in the first 2 years of antiretroviral therapy (ART). The decline is 1-2% greater with tenofovir (TDF) than other nucleos(t)ide reverse transcriptase inhibitors (NRTI). The effects of maraviroc (MVC) on BMD are unknown. We investigated a novel regimen containing MVC dosed 150mg once daily (QD).

Methods: A 48 wk double-blind, placebo-controlled trial was conducted at US ACTG sites. Subjects were HIV-1-infected, ART-naïve with viral load (VL) >1000 c/mL and R5 tropism on Trofile®. Exclusion criteria included any major NRTI or darunavir (DRV) mutation; active HBV infection; and CrCl ≤50 mL/min. Subjects were randomized 1:1 to MVC 150mg or TDF 300mg QD, stratified by VL< and ≥100,000 c/mL and age < and ≥30 yrs. All subjects received DRV 800mg, ritonavir (RTV) 100mg, and emtricitabine (FTC) 200mg QD. Dual-energy x-ray absorptiometry (DXA) scanning was done at baseline and wk48. Primary endpoint was percentage change in total hip BMD from baseline to wk48. Secondary endpoints included percentage change in lumbar spine BMD, time to virologic failure (VF), and change in CD4 count. VF was defined as confirmed VL >1000 c/mL at or after wk16 and before wk24, or confirmed VL > 200 c/mL at or after wk24. All analyses were as-treated. P-values were not adjusted for multiple comparisons.

Results: We enrolled 262 subjects. The analysis population (N=259; 130 MVC, 129 TDF) was 91% male; median age 33yrs, 45%White, 30%Black, 22%Hispanic. At baseline, median VL was 4.5 $\log_{10}$ c/mL and CD4 count was 390 cells/mm^3. Decline in hip BMD (as-treated N=115 for MVC, 109 for TDF) from baseline to wk48 was less with MVC: median (Q1, Q3) change in BMD of -1.51% (-2.93%, -0.11%) vs -2.40% (-4.30%, -1.32%) for TDF (Wilcoxon p<0.001). Median lumbar spine BMD decline was also less with MVC (-0.88% vs -2.35%, p<0.001). Virologic outcomes in both arms were good; VF probabilities by wk24 were 4% for MVC vs. 2% for TDF, and 5% vs. 3% by wk48 (MVC-TDF difference 2% (-4%, 5%). VL ≤50 c/mL was 85%MVC vs. 93%TDF at wk24 (p=0.06) and 94% in each arm at wk48 (p=0.89). CD4 change from baseline to wk48 was greater with MVC; median of +234 vs. +188 cells/mm^3, p=0.036. At wk48, CrCl was >90 mL/min in 90%MVC, 91%TDF. All results were similar with ITT analyses. Both regimens were well-tolerated

Conclusions: Initiating ART with QD MVC, FTC and DRV/RTV resulted in less bone loss compared to TDF-based therapy with no apparent difference in virologic efficacy. MVC may be an option to attenuate early bone-loss.

BACKGROUND

Bone mineral density (BMD) decreases by 2-6% in the first 2 years of antiretroviral therapy (ART). The decline is 1-2% greater with tenofovir (TDF) than other nucleos(t)ide reverse transcriptase inhibitors (NRTI). The effects of maraviroc (MVC) on BMD are unknown. We investigated a novel regimen containing MVC dosed 150 mg once daily (QD) compared to one containing TDF.

OBJECTIVES

The primary objective was to compare the effects of maraviroc vs. tenofovir containing regimens on bone mineral density (BMD).

Primary endpoint: Percentage change in total hip BMD from baseline to week 48
Secondary endpoints:
- Percentage change in lumbar spine BMD from baseline to week 48
- Time to virologic failure:
  - Confirmed HIV RNA >1000 copies/mL at or after week 16 and before week 24:
  - Confirmed HIV RNA > 200 copies/mL at or after week 24.
- Percentage with HIV RNA <50 copies/mL
- Change in CD4 count
- Adverse events

STATISTICAL ANALYSIS:

Primary analyses were as-treated; supportive analyses regardless of status on randomized treatment (ITT) were also performed. Within group changes were evaluated with Wilcoxon signed rank tests; between group comparisons used Wilcoxon rank sum tests. All analyses were stratified by age at study entry.

METHODS

DESIGN: A5303: Phase II, double-blind, placebo-controlled, randomized 48-week clinical trial conducted at 33 AIDS Clinical Trials Group (ACTG) and 4 Adolescent Trials Network sites

INTERVENTION: Subjects were randomized (1:1) to:

Maraviroc 150mg + tenofovir placebo (once daily)
vs.
Tenofovir 300mg + maraviroc placebo (once daily)

PLUS **Emtricitabine 200mg, Darunavir 800mg/ritonavir 100mg**

- Stratification by HIV-1 RNA < and ≥100,000 copies/mL, Age < and ≥30 yrs.
- Treatment for 48 weeks

ELIGIBILITY CRITERIA:
Inclusion:
- HIV-1-infected, men and women, 18 years and older
- Antiretroviral treatment-naïve
- R5 tropism on Trofile® phenotypic assay
- Plasma HIV-1 RNA ≥1,000 copies/mL

Exclusions:
- Any major NRTI or darunavir-resistance mutation
- Creatinine clearance (CrCl) ≤50 mL/min (based on the Cockcroft-Gault equation)
- Active hepatitis B infection
- History of bone fragility fracture
- Current or prior use of bisphosphonates, teriparatide, raloxifene, denosumab
- New hormonal therapy within 6 month, steroids within 30 days

EVALUATIONS: Entry, Week 4, 16, 24, 36, 48
- Dual-energy X-ray absorptiometry (DXA) scan of the left hip and lumbar spine (L1 – L4)
  - Baseline and week 48
  - Central reading of BMD at Tufts Body Composition Analysis Center
- Plasma HIV-1 RNA (Abbott RealTime Assay, lower limit of detection 40 copies/mL)
  - Suspected VF was confirmed within 30 days of receiving result
- CD4, hematology, liver function tests, blood chemistries, serum creatinine

DISPOSITION OF STUDY SUBJECTS (N = 262)

Allocated to MVC with DRV/r and FTC (n=130)	Allocated to TDF with DRV/r and FTC(n=132)
	• Did not receive study treatment (n=3)

• Completed study on randomized treatment (n=119)
  • Completed study off randomized treatment (n=1)
  • Failed to complete study (n=10)
	• Completed study on randomized treatment (n=112)
	  • Completed study off randomized treatment (n=3)
	  • Failed to complete study (n=17)

• As-treated primary analysis for change in hip BMD from baseline to week 48 (n=115)
  o Missing week 48 DXA (n=4)
	• As-treated primary analysis for change in hip BMD from baseline to week 48 (n=109)
	  o Missing/poor DXA (n=2)
	  o Received prohibited medication (n=1)

RESULTS

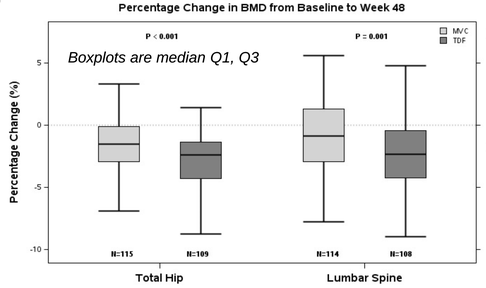
Table 1: Baseline Characteristics and Bone Mineral Density

Characteristic		MVC (n = 130)	TDF (n = 129)	Total (N = 259)
Age (years)	Median (Q1, Q3) < 30 (n,%) ≥30 (n,%)	33 (26, 42) 49 (38%) 81 (62%)	33 (26, 42) 48 (37%) 81 (63%)	33 (26, 42) 97 (37%) 162 (63%)
Sex, n (%)	Male Female	115 (88%) 15 (12%)	120 (93%) 9 (7%)	235 (91%) 24 (9%)
Race/ethnicity, n (%)	White non-Hispanic Black non-Hispanic Hispanic Other	57 (44%) 45 (35%) 24 (18%) 4 (4%)	59 (46%) 33 (26%) 34 (26%) 3 (3%)	116 (45%) 78 (30%) 58 (22%) 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, n (%) ≥100,000, n (%)	92 (71%) 38 (29%)	102 (80%) 26 (21%)	194 (75%) 64 (25%)
CD4 count (cells/mm^3)	Median (Q1, Q3)	389 (295, 496)	392 (290, 518)	390 (294, 517)
Hepatitis C antibody	Positive, n (%)	10 (8%)	12 (9%)	22 (8%)
Creatinine clearance (mL/min)	Median (Q1, Q3) >90, %	124 (105, 152) 90%	126 (106, 139) 89%	124 (106, 145) 90%
Body mass index (kg/m^2)	Median (Q1, Q3)	25 (22, 29)	26 (23, 29)	25 (23, 29)
Bone Mineral Density (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)

Table 2: Percent changes in Bone Mineral Density from Baseline to Week 48 (As-treated)

	Treatment Arm	N	Median (Q1, Q3)	95% CI for Median	p-value (within group)[a]	p-value (between group)[b]
Total Hip BMD	MVC	115	-1.51 (-2.93, -0.11)	(-1.84, -1.01)	<0.001	<0.001
	TDF	109	-2.40 (-4.30, -1.32)	(-2.99, -1.85)	<0.001	
Lumbar Spine BMD	MVC	114	-0.88 (-2.93, 1.30)	(-1.50, -0.42)	<0.001	0.001
	TDF	108	-2.35 (-4.25, -0.45)	(-3.20, -1.57)	<0.001	

[a] *Wilcoxon signed rank test was used to test the within treatment group changes or percentage changes from baseline*
[b] *Stratified Wilcoxon rank sum tests were used to test for differences between the two treatment groups, stratified by the age stratum*



- **Decline in hip and lumbar spine BMD from baseline to week 48 was less with MVC**
- Post hoc analysis showed greater reduction in hip BMD with MVC compared to TDF in non-hispanic Blacks (data not shown)

RESULTS

Table 3: Probability of Virologic Failure while on Randomized Treatment and Proportion with HIV-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%
			Between arm difference (MVC-TDF) at 24 wks		
			(0%, 16%)	(0%, 16%)	(-5%, 13%)
Between arm difference (MVC-TDF) by 48wks [b]			Between arm difference (MVC-TDF) at 48 wks		
		2% (-4%, 5%)	(-7%, 6%)	(-8%, 6%)	(-15%, 4%)

[a] *Product-limit estimates*
[b] *95% CI for between arm differences (MVC-TDF) in cumulative probability of VF by week 48, stratified by screening RNA stratum.*

CD4

CD4 change from baseline to week 48 was greater with MVC than TDF; median of +234 (131,327) vs. +188 (94,304) cells/mm^3, p=0.036.

SAFETY AND TOLERABILITY

At week 48, CrCl was >90 mL/min in 90% MVC, 91% TDF.
Both regimens were well-tolerated. Grade 3 adverse events (AE) occurred in 10% of subjects on the MVC arm and 14% on TDF, while 2% and 3%, respectively, experienced grade 4 AEs.

CONCLUSIONS

- **Initiating ART with maraviroc 150 mg, emtricitabine and darunivir/ritonavir resulted in less bone loss compared to tenofovir-based therapy**
- **There was no apparent difference in virologic efficacy and both regimens were well tolerated.**
- **MVC may be an option to attenuate early bone-loss.**

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