

Differential Effects of MK-0518 and Efavirenz on Serum Lipids and Lipoproteins in Antiretroviral Therapy (ART)-naïve Patients (24 Week Results)

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ABSTRACT

Background. Some antiretroviral agents are associated with hyperlipidemia.

Objectives. To evaluate serum lipids during MK-0518 therapy.

Methods. Phase II study evaluating 4 doses of MK-0518, a novel HIV integrase inhibitor, vs efavirenz (EFV), both combined with tenofovir/lamivudine (TFV/3TC), in ART-naïve HIV-infected patients (pts) with HIV-1 RNA ≥ 5000 copies/mL and CD4 cells ≥ 100 /uL. Changes from baseline in fasting serum cholesterol (SC), triglycerides (TG), LDL-C and HDL-C after 24 weeks treatment were evaluated.

Results. Baseline lipids were similar in all treatment groups. Mean changes from baseline in serum lipids (mg/dL) at 24 weeks are:

	Treatment**	N	Baseline	Change (95% CI)
SC	MK-0518 100 mg bid	39	168	-7* (-14, 0)
	MK-0518 200 mg bid	34	161	-2* (-11, 8)
	MK-0518 400 mg bid	40	168	-7* (-15, 2)
	MK-0518 600 mg bid	35	162	-4* (-12, 5)
	Efavirenz 600 mg qd	36	170	+19 (8, 30)
TG	MK-0518 100 mg bid	39	129	+2 (-22, 26)
	MK-0518 200 mg bid	34	110	-5* (-20, 9)
	MK-0518 400 mg bid	40	127	-2* (-23, 18)
	MK-0518 600 mg bid	35	155	-43* (-87, 1)
	Efavirenz 600 mg qd	36	128	+47 (-1, 96)

N= number of patients with data
*p-value < 0.05 for comparison to efavirenz
**MK-0518 and EFV were given in combination with TFV/3TC

SC and TG values were relatively unchanged following MK-0518 therapy. In contrast, efavirenz treatment was associated with increases in both SC and TG. Effects on LDL-C and HDL-C will be presented.

Conclusions. MK-0518, in combination with TFV/3TC, had no adverse effects in serum lipids at 24-weeks.

BACKGROUND

• Elevated serum cholesterol (SC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C) and decreased high density lipoprotein cholesterol (HDL-C) are often associated with antiretroviral therapy (ART) and may confer increased risk for cardiovascular disease and stroke (Int J STD AIDS 2005; 16 (Suppl. 1): 2-13).

- MK-0518: a novel HIV integrase inhibitor
 - HIV integrase inhibition: a new mechanism of action
 - Potent antiviral activity in combination therapy
 - In ART-naïve patients at Week 24 (Markowitz et al, IAC 2006, Abst THLB0214)
 - 85 – 95% with HIV RNA < 50 copies/mL
 - In patients failing therapy with triple class resistant virus at Week 16 (Grinsztejn et al, CROI 2006, Abst 159LB)
 - 56 – 72% with HIV RNA < 50 copies/mL*

* See ICAAC 2006 Abstract # H-1670b

BACKGROUND (CONT.)

Protocol 004 Study Design

- Randomized, double-blind, dose - ranging study to evaluate the safety and efficacy of MK-0518 given at 100, 200, 400 or 600 mg b.i.d. versus efavirenz 600 mg q.d., both in combination with tenofovir (TFV) and lamivudine (3TC).

- Key inclusion criteria:
 - Susceptible to efavirenz (EFV), lamivudine (3TC), and tenofovir (TFV) (determined by genotype)
 - No prior ART (<7 days OK)
 - HIV RNA ≥ 5000 copies/mL
 - CD4 ≥ 100 cells/mm³

- Key Endpoints:
 - HIV RNA, CD4 counts, at week 12, 24, 48
 - Safety: labs and adverse experiences

- Exploratory Endpoint:
 - Serum lipid levels at week 12, 24, 48
 - METHODS: All analyses were performed on fasting samples in a blinded manner by Covance, Inc. (Princeton, NJ) as part of a CDC lipid panel. Serum concentrations of total cholesterol (SC) and triglycerides (TG) and HDL-C were determined using automated enzymatic assays. HDL-C concentrations were determined after precipitation of the non-HDL fraction with dextran sulfate. LDL-C was calculated using the Friedewald formula.
 - 12 and 24 week data available

- Statistical methods
 - Changes from baseline in lipid levels were calculated by treatment group based upon observed data. Two-sided confidence intervals and p-values were computed using normal approximation.

RESULTS

Baseline Patient Characteristics

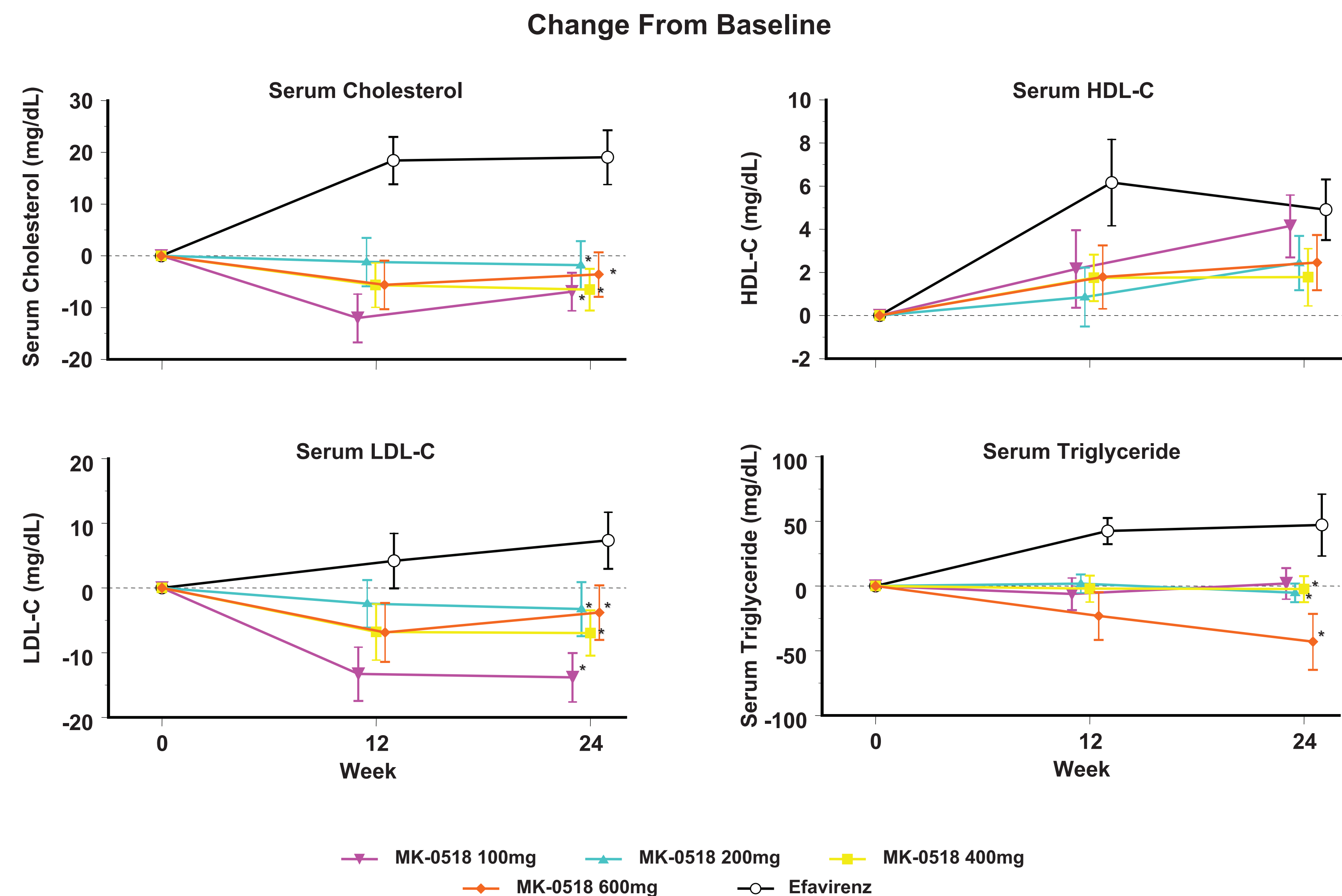
	MK-0518 bid*				Efavirenz* 600mg qd N=38
	100 mg N=39	200 mg N=40	400 mg N=41	600 mg N=40	
Age-mean (yrs)	37	34	36	37	36
%Male	85	73	90	73	76
%Non-White	82	65	66	65	68
HIV RNA copies/ml** (log ₁₀ copies/ml)	58206 (4.8)	64715 (4.8)	43083 (4.6)	57919 (4.8)	67554 (4.8)
CD4 – mean (cells/ul)	314	296	338	271	280
% with AIDS	31	33	29	43	37

* With TFV/3TC ** = geometric mean

Baseline Serum Lipid Parameters (mean)

	MK-0518 bid*				Efavirenz* 600mg qd (n) (mg/dl)
	100 mg (n) (mg/dl)	200 mg (n) (mg/dl)	400 mg (n) (mg/dl)	600 mg (n) (mg/dl)	
Cholesterol	(39) 168	(34) 161	(40) 168	(35) 162	(36) 170
LDL-C	(36) 108	(34) 100	(40) 104	(33) 101	(33) 108
HDL-C	(39) 38	(34) 38	(40) 38	(35) 37	(35) 37
Triglycerides	(39) 129	(34) 110	(40) 127	(35) 155	(36) 128

* With TFV/3TC



Each group dosed in combination with TFV/3TC *p<0.05 for comparison to efavirenz
Note: Due to limited sample volume, n was reduced by up to 6 per group per test.

CONCLUSION

- MK-0518, when dosed at 100 mg to 600 mg b.i.d. in combination with TFV/3TC for 24 weeks in treatment-naïve HIV infected patients:
 - was not associated with increases in SC, LDL-C, or TG, which contrasts significantly with lipid changes associated with treatment with efavirenz.

²Protocol 004 Study Team

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