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Fasted Lipid Changes after Administration of Maraviroc or Efavirenz in Combination with Zidovudine and Lamivudine (Combivir) for 48 Weeks to Treatment-naive HIV-infected Patients

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Background

- HIV/AIDS has become a chronic disease, with therapy that can last decades. A consideration when making treatment choices is that some approved therapies have been associated with dyslipidemia, which may adversely impact cardiovascular risk.[1]
- Maraviroc is the first approved CCR5 antagonist and the only oral entry inhibitor, and has a new mechanism of action compared to other approved antiretroviral agents. The lipid effects of CCR5 antagonists are less well characterized.
- Studies of humans with the CCR5 delta 32 deletion, which is associated with reduced cell-surface expression of CCR5 receptors, have shown that these individuals have a lower incidence of early myocardial infarction[2] and a lower risk of severe coronary artery disease.[3] Furthermore, mice at risk for atherosclerosis that were treated with a CCR5 antagonist showed delayed progression of atherosclerosis compared to untreated mice.[4,5] However, the relevance of these mouse model data to CCR5 antagonism in humans is unclear.
- The MERIT study was designed to compare the safety and efficacy of maraviroc (MVC) versus efavirenz (EFV), both administered with Combivir (CBV; a fixed-dose combination of zidovudine and lamivudine), in antiretroviral (ARV)-naive patients with R5 HIV-1 by the Trofile™ assay (Monogram Biosciences, South San Francisco, CA).[6] Analysis of Week 48 data demonstrated that 65% of patients receiving maraviroc achieved an HIV-1 RNA level of <50 copies/mL compared to 69% for efavirenz. More patients discontinued from maraviroc for lack of efficacy compared to efavirenz (11.9% versus 4.2%), whereas fewer patients discontinued maraviroc due to adverse events (4.2% versus 13.6%).
- The MERIT study design included a fasting metabolic assessment at baseline and at Weeks 24 and 48 or at early study discontinuation.

Objectives

- To evaluate the fasted lipid values in the MERIT study and their potential effect on cardiovascular risk.

Methods

- MERIT is an ongoing, double-blind, randomized, multinational trial comparing the safety and efficacy of maraviroc 300 mg BID vs efavirenz 600 mg QD, both in combination with Combivir (zidovudine/lamivudine), in ARV-naive adult patients infected with only R5 HIV (Trofile™ assay).
- Patients experiencing toxicity to zidovudine or lamivudine were permitted to substitute an alternative NRTI.
- A fasting lipoprotein profile was obtained for each patient at baseline, Week 24, and Week 48, or at early termination.
- Median maximum changes in total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, triglycerides (TG), calculated low-density lipoprotein (LDL) cholesterol, and total cholesterol/HDL ratio, as well as the proportion of patients in each treatment arm exceeding cutpoints identified in National Cholesterol Education Program (NCEP) ATP III clinical guidelines,[7] were compared between groups.
- Overall cardiovascular disease risk was assessed for each patient using the Framingham equation (http://hp2010.nhlbihin.net/atpiii/calculator.asp), which uses total cholesterol, HDL cholesterol, age, sex, smoking status, and use or nonuse of antihypertensive therapy (when systolic blood pressure is >120 mm/Hg) as variables to estimate 10-year absolute coronary heart disease (CHD) risk.
  - Because data on smoking status were not collected in the study, CHD risk was compared between treatment groups according to different smoking rate scenarios. For a 50% smoking rate scenario (which approximates to the smoking rate seen in the DAD Study[9]), smoking status (yes/no) was randomly imputed to the study population 500 times, by sampling from a binomial distribution with a probability of success of 0.5. Smoking status was assumed to remain constant for the duration of the study.

Results

- A total of 721 patients at study centers in North America, Europe, South America, South Africa, and Australia were randomized and received at least one dose of study medication. Baseline characteristics were comparable between treatment groups (Table 1).

Table 1. Baseline characteristics*

	EFV + CBV (N=361)	MVC + CBV (N=360)
Age, years	37 (30, 43)	35.5 (30, 43)
Male, n (%)	259 (71.7)	256 (71.1)
Race, n (%)		
White	198 (54.8)	204 (56.7)
Black	133 (36.8)	123 (34.2)
Asian	5 (1.4)	6 (1.7)
Other	25 (6.9)	27 (7.5)
Bodyweight, kg	70.7 (62.5, 80.1)	72.3 (62.6, 80.8)
Diabetes mellitus, n (%)	6 (1.7)	5 (1.4)
Supine systolic blood pressure, mm/Hg	124 (116, 131)	123 (114, 132)
Supine diastolic blood pressure, mm/Hg	76 (70, 83)	77 (70, 84)
HIV-1 RNA, $\log_{10}$ copies/mL	4.9 (4.5, 5.2)	4.9 (4.4, 5.3)
CD4+ count, cells/mm^3	259 (189, 327)	244 (176, 320)

* Values are median (lower quartile, upper quartile), unless otherwise stated

Baseline fasting lipid values were not significantly different between treatment groups (Table 2). Approximately one in seven patients in each arm had a total cholesterol level ≥200 mg/dL. A similar proportion of patients had a triglyceride level ≥200 mg/dL.

- Five patients in a efavirenz arm and 11 patients in the maraviroc arm had LDL cholesterol values ≥160 mg/dL at baseline.
  - *This is the threshold at which the NCEP guidelines recommend considering LDL-lowering therapy in patients who have ≥2 risk factors for CHD (e.g. hypertension, family history of premature CHD, older age, smoker) and a* ***<10%*** *10-year risk for CHD.*
- Thirty-one patients in the efavirenz arm and 42 in the maraviroc arm had LDL cholesterol values ≥130 mg/dL at baseline.
  - *This is the threshold at which the NCEP guidelines recommend considering LDL-lowering therapy in patients who have ≥2 risk factors for CHD and a* ***10–20%*** *10-year risk for CHD.*
- Three patients in the efavirenz arm and five patients in the maraviroc arm were receiving LDL-lowering therapy at baseline. These patients, and patients who initiated LDL-lowering therapy during the study, were included in all the analyses presented here.

Table 2. Baseline fasting lipid characteristics

	Median (lower quartile, upper quartile)		Patients exceeding NCEP lipid cutpoints,[7] n (%)	
	EFV + CBV (N=361)	MVC + CBV (N=360)	EFV + CBV (N =361)	MVC + CBV (N=360)
Total cholesterol (TC), mg/dL	155 (131, 178)	156 (131,181)	46 (12.8)†	50 (14.1)†
LDL cholesterol, mg/dL	88 (70, 111)	92 (71, 114)	31 (8.9)† 5 (1.4)‡	42 (12.1)† 11 (3.2)‡
HDL cholesterol, mg/dL	38 (32, 46)	37 (31, 46)	N/A	N/A
TC:HDL cholesterol	4.0 (3.2, 4.9)	4.2 (3.4, 5.0)	N/A	N/A
Triglycerides (TG), mg/dL	104 (73, 162)	106 (76, 153)	51 (14.2)‡	48 (13.5)‡

Baseline values were missing for up to 13 patients in each treatment group
† Patients exceeding 'borderline-high' cutpoint (TC ≥200 mg/dL [≥5.2 mmol/L]; LDL ≥130 mg/dL [≥3.4 mmol/L])
‡ Patients exceeding 'high' cutpoint (LDL ≥160 mg/dL [≥4.1 mmol/L]; TG ≥200 mg/dL [≥2.3 mmol/L])

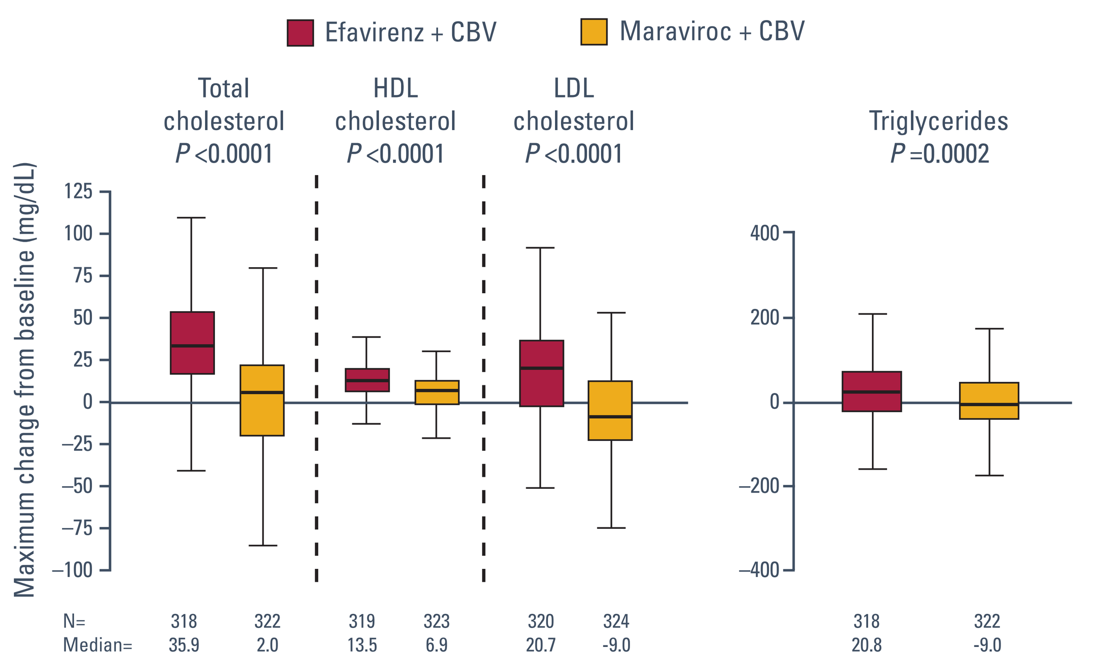
On-treatment NRTI substitutions

- A total of seven (1.9%) patients in the maraviroc arm and ten (2.9%) in the efavirenz arm changed their NRTIs from Combivir to Truvada (a fixed-dose combination of tenofovir and emtricitabine).

On-treatment changes in fasting lipid parameters

- The median maximum changes from baseline in total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels were significantly greater in the efavirenz treatment group than in the maraviroc group (Figure 1).
- The median decrease in the total cholesterol/HDL ratio was greater in the maraviroc group than in the efavirenz group (–0.54 vs –0.43, respectively; P=0.005).

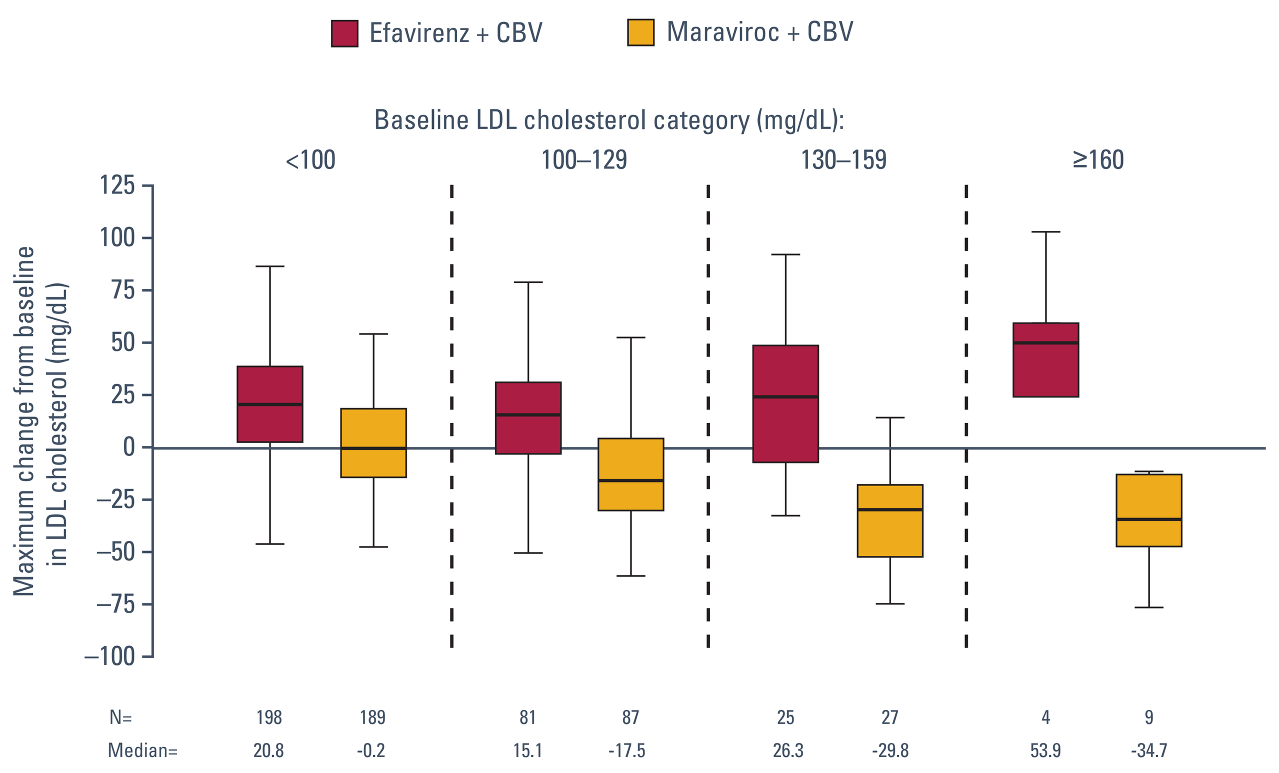
Figure 1. Median maximum change from baseline in lipid parameters



The boxes represent the interquartile range (IQR) from 25th to 75th percentile, while the horizontal black line in the box represents the median value. The whiskers extend to the most extreme data point within 1.5x the IQR from the box.
P-values are for comparisons of medians (Wilcoxon Rank-Sum test)
(To convert cholesterol to mmol/L, divide values by 38.7; to convert triglyceride values to mmol/L, divide by 88.6)

- While for efavirenz the change in LDL cholesterol was directly related to baseline LDL cholesterol, for maraviroc the change in LDL cholesterol was inversely related to baseline LDL cholesterol (Figure 2).

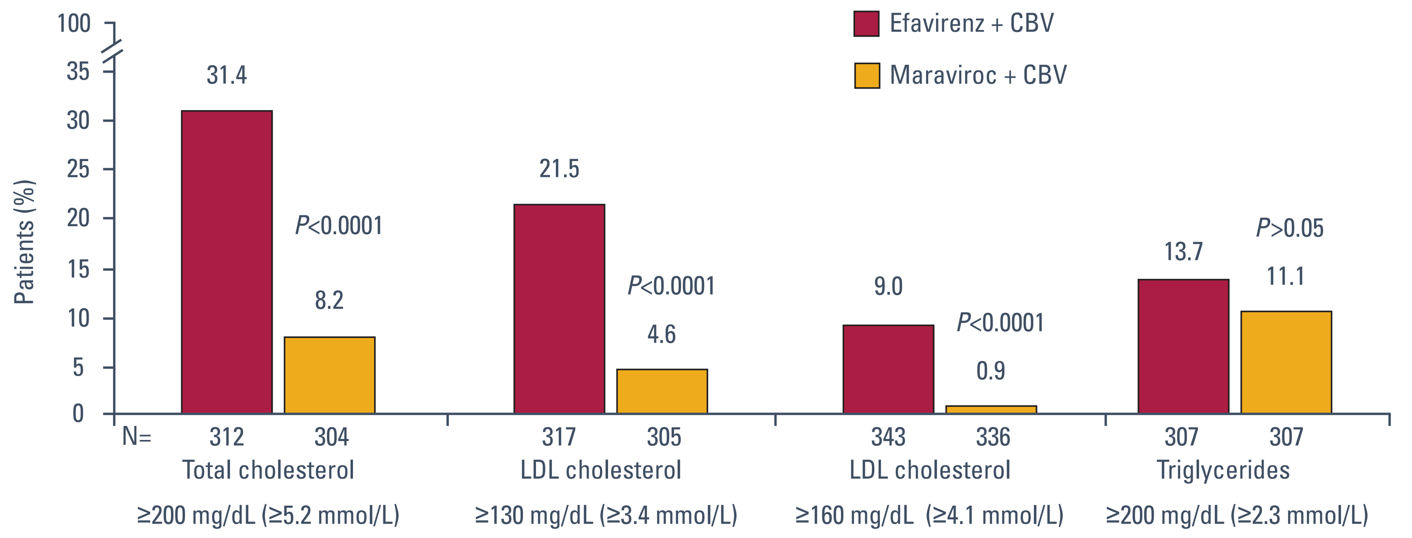
Figure 2. Median maximum change from baseline in LDL cholesterol levels by baseline NCEP LDL cholesterol category



A greater percentage of patients receiving efavirenz therapy experienced increases in total cholesterol and LDL cholesterol levels at some point after baseline to ≥130 mg/dL, compared to those receiving maraviroc therapy (P<0.0001) (Figure 3).

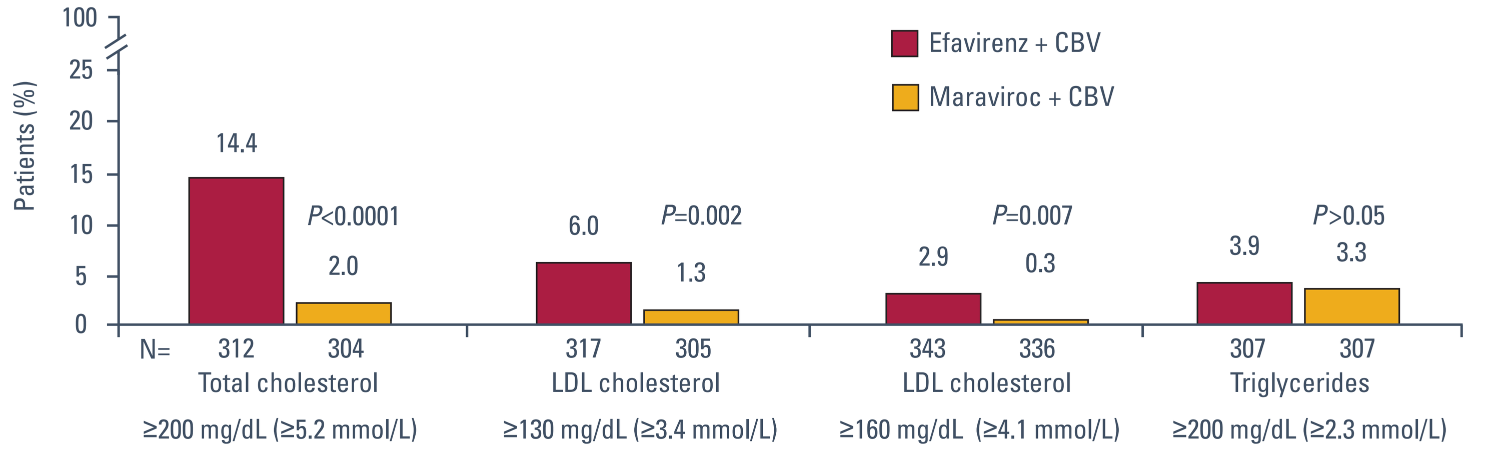
- 31/343 (9%) patients receiving efavirenz versus 3/336 (0.9%) patients receiving maraviroc developed LDL cholesterol levels during the study that were ≥160 mg/dL (P<0.0001).
- Similarly, the proportions of patients that exceeded these cutpoints at both Weeks 24 and 48 were higher in the efavirenz group than in the maraviroc group (P<0.0001 for total cholesterol and P=0.002 for LDL cholesterol) (Figure 4).
  - 10/343 (2.9%) patients in the efavirenz arm versus 1/336 (0.3%) patients in the maraviroc arm had high on-treatment LDL cholesterol levels (≥160 mg/dL) at both Week 24 and Week 48 (P=0.007).
- These analyses did not include patients whose lipid levels already exceeded the thresholds at baseline.
- A similar, low number of patients in each treatment group (six patients in the efavirenz arm and three patients in the maraviroc arm) initiated LDL-lowering therapy during the study.

Figure 3. Percentage of patients whose lipid values exceeded cutpoints for starting LDL-lowering therapy (according to NCEP guidelines) at one or more on-study assessments*



Analysis excludes those patients whose value exceeded the threshold at baseline
P-values are for comparisons of proportions (Pearson's chi-square test)
*Fasting lipoprotein profiles were obtained for each patient at Week 24 and Week 48, or at early termination

Figure 4. Percentage of patients who exceeded cutpoints for starting LDL-lowering therapy (according to NCEP guidelines) at both Week 24 AND Week 48

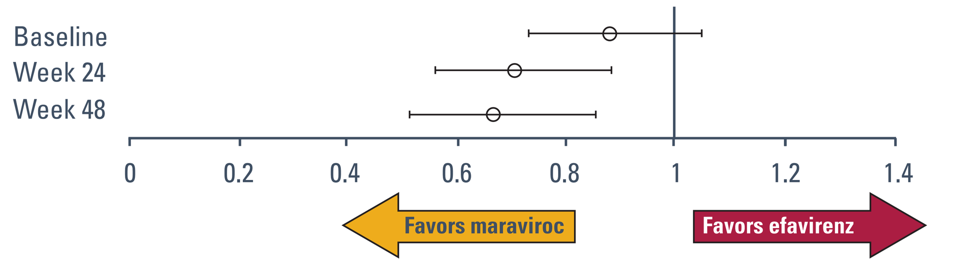


Analysis excludes those patients whose value exceeded the threshold at baseline

Cardiovascular disease risk

- The relative risk of having a CHD event within 10 years for the two treatment groups, assuming a population smoking rate of 50% *(see Methods)*, is shown in Figure 5. The risk was consistently higher in the efavirenz treatment group than in the maraviroc group at Week 24 and Week 48.
- The absolute CHD 10-year risk (mean [SD]) in the maraviroc and efavirenz treatment groups was 2.1% (3.3%) and 3.0% (4.7%) at Week 24 and 2.2% (3.7%) and 3.3% (5.1%) at Week 48, respectively.

Figure 5. Relative risk (and 95% confidence intervals) of having a CHD event within 10 years (Framingham equation) at a simulated smoking rate of 50%



Conclusions

- At 48 weeks, increases from baseline in total cholesterol, LDL cholesterol, and triglycerides were significantly greater for patients receiving efavirenz + Combivir than for those receiving maraviroc + Combivir, with a higher proportion of efavirenz patients experiencing lipid levels above those recommended by NCEP guidelines. High LDL cholesterol levels and elevated triglycerides are both independent risk factors for cardiovascular disease.[7]
  - HDL cholesterol levels improved in both treatment groups. The median maximum increase was significantly greater in the efavirenz group than in the maraviroc group. However, the benefits of increasing HDL cholesterol levels independent of reductions in LDL cholesterol or triglyceride levels, in terms of reducing major cardiovascular outcomes, have not been proven.[10]
- There was a small but significant difference in total cholesterol/HDL ratios which decreased more from baseline in patients receiving maraviroc + Combivir than in those receiving efavirenz + Combivir.
- The use of LDL-lowering therapy was infrequent and similar between the two treatment groups.
- These data demonstrate that maraviroc has no negative impact on lipid profiles, and appears to have reduced the total cholesterol/HDL ratio. Overall, maraviroc is at least as lipid neutral as efavirenz and may offer some advantages compared to efavirenz, for example in those patients with elevated LDL cholesterol levels prior to treatment. Whether maraviroc will be associated with decreased progression of atherosclerosis in humans that is independent of lipid effects, as seen in the mouse model,[4] remains to be determined.

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