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MAJOR ARTICLE

Changes in Liver Steatosis After Switching From Efavirenz to Raltegravir Among Human Immunodeficiency Virus–Infected Patients With Nonalcoholic Fatty Liver Disease

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Background. Antiretroviral drugs with a lower potential to induce hepatic steatosis in human immunodeficiency virus (HIV) infection need to be identified. We compared the effect of switching efavirenz (EFV) to raltegravir (RAL) on hepatic steatosis among HIV-infected patients with nonalcoholic fatty liver disease (NAFLD) receiving EFV plus 2 nucleoside analogues.

Methods. HIV-infected patients on EFV plus tenofovir/emtricitabine or abacavir/lamivudine with NAFLD were randomized 1:1 to switch from EFV to RAL (400 mg twice daily), maintaining nucleoside analogues unchanged, or to continue with EFV plus 2 nucleoside analogues. At baseline, eligible patients should show controlled attenuation parameter (CAP) values ≥238 dB/m. Changes in hepatic steatosis at 48 weeks of follow-up over baseline levels were measured by CAP.

Results. Overall, 39 patients were included, and 19 of them were randomized to switch to RAL. At week 48, median CAP for the RAL group was 250 (Q1–Q3, 221–277) dB/m and 286 (Q1–Q3, 269–314) dB/m for the EFV group ($P = .035$). The median decrease in CAP values was −20 (Q1–Q3, −67 to 15) dB/m for the RAL arm and 30 (Q1–Q3, −17 to 49) dB/m for the EFV group ($P = .011$). CAP values <238 dB/m at week 48 were observed in 9 (47%) patients on RAL and 3 (15%) individuals on EFV ($P = .029$).

Conclusions. After 48 weeks, HIV-infected individuals switching EFV to RAL showed decreases in the degree of hepatic steatosis, as measured by CAP, compared with those continuing with EFV. In addition, the proportion of patients without significant hepatic steatosis after 48 weeks was greater for those who switched to RAL.

Clinical Trials Registration. NCT01900015.

Keywords. HIV; nonalcoholic fatty liver disease; efavirenz; raltegravir.

Nonalcoholic fatty liver disease (NAFLD) is frequently observed in human immunodeficiency virus (HIV)–infected patients [1–4]. NAFLD itself can promote fibrosis progression, evolving to steatohepatitis, on which cirrhosis may develop and hepatocellular carcinoma emerge [5–7]. Hepatic steatosis is linked with metabolic disorders and exposure to certain antiretroviral drugs [1–4, 8–11]. The main potential mechanism involved in antiretroviral drug–related hepatic steatosis seems to be mitochondrial toxicity. Thus, the use of nucleoside analogues associated with more severe mitochondrial toxicity, such as dideoxynucleoside analogues, has been linked with hepatic steatosis [1, 8–11]. Efavirenz (EFV) has been related with clinical manifestations of mitochondrial toxicity, such as lipoatrophy [12]. Likewise, EFV enhances fatty accumulation in hepatocyte cell lines in vitro [13]. Moreover, the cumulative use of EFV seemed to be associated with an increased risk of hepatic steatosis progression in HIV/hepatitis C virus (HCV)–coinfected patients [8].

Given the potential of NAFLD for causing advanced liver disease, the effects of antiretroviral drug regimens less likely to induce increases in hepatic steatosis need to be investigated. Drug combinations based on raltegravir (RAL) may fulfill that requirement. Thus far, RAL does not induce mitochondrial toxicity [14] and has demonstrated a safe metabolic profile [14–20]. Cross-sectional and longitudinal observational data indicate that metabolic factors are the strongest predictors of hepatic steatosis in HIV infection [3, 4, 21]. In addition, use of RAL was associated with a trend to lower frequency of hepatic steatosis [3] and lesser likelihood of progression of hepatic steatosis [21], but these associations did not stand up after controlling for metabolic factors. Therefore, the role of RAL preventing the

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progression of hepatic steatosis, which could be driven by its metabolic safety profile, needs to be clarified in controlled, prospective studies. Because of these issues, in this trial we aimed at comparing the impact of switching from EFV to RAL in patients receiving EFV plus 2 nucleoside analogues vs continuing with the same therapy on hepatic steatosis as measured by controlled attenuation parameter (CAP) among HIV-infected patients with NAFLD.

PATIENTS AND METHODS

Trial Design

This was a phase 4, multicenter, open-label, randomized 48-week study to evaluate changes in hepatic steatosis by CAP measurements after switching to RAL or maintaining the EFV-based regimen in HIV-infected patients with NAFLD. Patients on EFV plus 2 nucleoside analogues, either tenofovir/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC), were randomized 1:1 to switch from EFV to RAL 400 mg twice daily, maintaining the nucleoside analogues unchanged, or to continue the same combination of EFV plus 2 nucleoside analogues. The trial was initially designed to recruit only patients with detectable plasma HCV RNA without foreseeable anti-HCV treatment during the study period. The availability of rapid interferon-free drug regimens in Spain meant that most HIV/HCV-coinfected patients could be considered candidates for anti-HCV therapy. Due to this fact, and given that the prevalence of and associations with hepatic steatosis for HIV-infected patients with and without HCV coinfection were similar [3], and that the rates of and risk factors for progression of hepatic steatosis were comparable between patients with and without HCV coinfection [21], a major amendment was presented to and approved by the regulatory authorities on March 2015 to allow the inclusion of patients without active HCV coinfection.

The estimated simple size for this trial was 43 patients per arm. This size would have been sufficient to achieve a statistical power of 80% to detect a difference of 20 dB/m between arms, with a bilateral 95% confidence interval (CI). However, because the rate of recruitment was lower than expected, and an intermediate analysis, planned for when half of the patients were included, proved differences in the primary variable, the inclusion of patients was stopped before reaching the estimated sample size.

Patients

Between February 2014 and September 2015, HIV-infected patients were enrolled at 8 clinical sites in Spain. Inclusion criteria were (1) age ≥18 years; (2) receiving treatment with EFV plus TDF/FTC or ABC/3TC for the last ≥6 months; (3) plasma HIV RNA <50 copies/mL for ≥24 weeks documented in at least 2 clinical visits; (4) a CAP measurement ≥238 dB/m, indicative of the presence of hepatic steatosis involving >10% of hepatocytes; and (5) self-reported average daily alcohol intake <50 g for men and <40 g for women. Patients could be coinfected by HCV, as documented by detectable plasma HCV RNA, or not. Exclusion criteria were any of the following: (1) pregnancy; (2) history of antiretroviral drug failure or documented HIV resistance; (3) an AIDS-defining opportunistic disease in the 24 weeks before recruitment; (4) history of malignant neoplasia; (5) active illicit drug use or any other condition that might compromise the study drug adherence in the opinion of the investigators.

Study Assessments

Clinical visits were scheduled at baseline, week 4, week 12, and every 12 weeks thereafter until week 48. Body mass index (BMI) and waist-to-hip ratio were calculated at baseline, week 24, and week 48. Laboratory tests for hematology, blood chemistry, CD4 cell counts, and plasma HIV RNA were drawn at each visit. CAP and liver stiffness measurements were acquired at baseline, week 24, and week 48. Safety was assessed through the reporting of clinical adverse events and laboratory abnormalities. The severity of adverse events was evaluated according to the Division of AIDS toxicity table [22].

CAP and liver stiffness were measured using a commercially available elastography device with the standard M probe (FibroScan 502, Echosens, Paris, France). An experienced operator who was blinded for the therapy regimen performed the elastographic measurements. Elastography examinations were conducted following a standardized procedure [23]. Determinations were considered as valid if at least 10 successful measurements could be achieved, with an interquartile range <30% of the median liver stiffness value and a success rate >60%.

CAP is an estimate of the total ultrasonic attenuation and it is expressed as decibels per meter (dB/m). A cutoff of 238 dB/m was selected to define the presence of significant hepatic steatosis (steatosis involving ≥10% of hepatocytes). This figure was considered the optimal cutoff to discriminate hepatic steatosis affecting ≥10% hepatocytes by Sasso et al [23]. This cutoff exhibits positive and negative predictive values of 0.871 and 0.867, respectively.

Study Oversight

The study was reviewed and approved by the Spanish Agency of Medicines and was registered with the European Clinical Trials Database (EudraCT 2013-002111-10). It was also registered at ClinicalTrials.gov (NCT01900015). The study was conducted in compliance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, as defined by the International Conference on Harmonisation and according to the ethical principles of the European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The study protocol was approved by the institutional review board or independent ethics committee at each site. All patients provided their written informed consent to participate.

Analysis of Data

The primary study variable was the median value of CAP after 48 weeks of follow-up. The median value of CAP at 48 weeks was compared between arms. The median decline in this parameter observed during follow-up was also compared between groups.

A descriptive and exploratory analysis of data was carried out. The χ^2 or Fisher exact test was used to compare proportions between treatment groups. Mann-Whitney *U* test was applied for comparisons of continuous variables between groups. Comparisons were made with use of a 2-sided α level of .05. Statistical analysis was performed using IBM SPSS version 23.0 software (IBM Corp, Somers, New York).

RESULTS

Characteristics of the Study Population

One hundred twenty-seven patients were evaluated for the presence of hepatic steatosis; 47 (37%) of them showed CAP ≥238 dB/m. The disposition of those patients is summarized in Figure 1. Of 47 patients included in the study, 24 of them were randomized to switch EFV by RAL and 23 of them were randomized to continue with the prior EFV-based regimen. Two (8.3%) patients in the RAL arm started anti-HCV therapy before reaching week 48 and were excluded. Three (12.5%) patients in the RAL arm and 3 (15%) patients in the EFV group were lost to follow-up. Thus, 19 patients randomized to switch to RAL and 20 patients randomized to continue on EFV constituted the study population. The baseline characteristics of the study population are summarized in Table 1. The duration of antiretroviral therapy before baseline was 120 (88–132) months for patients assigned to the RAL group and 122 (100–151) for those randomized to the EFV group (P = .351). The time on EFV before baseline is shown in Table 1. Among patients with active HCV infection, 12 (86%) individuals were infected by genotype 1 or 4 and 2 (14%) by genotype 3 in the RAL group, compared with 11 (92%) patients infected by genotype 1 or 4 and 1 (8%) by genotype 3 in the EFV group (P = .347). Eight patients achieved sustained virological response with anti-HCV treatment before randomization: 5 (26%) individuals in the RAL group and 3 (15%) in the EFV group (P = .451). The median time since HCV clearance with treatment until the baseline date was 76 (Q1–Q3, 54–104) months and 122 (Q1–Q3, 90–123) months for the RAL and EFV groups, respectively (P = .250).

The BMI was >18 kg/m^2 and <25 kg/m^2 in 7 (37%) patients in the RAL group and 9 (45%) individuals in the EFV arm. A BMI ≥30 kg/m^2 was observed in 5 (26%) patients in the RAL group and in no individual in the EFV arm (P = .020). Fasting plasma glucose level >100 mg/dL was found in 8 (42%) patients in the RAL group and 7 (35%) individuals in the EFV arm (P = .648). Five (26%) patients switched to RAL vs 4 (20%) of those continued on EFV showed blood triglycerides ≥150 mg/dL (P = .640). Blood high-density lipoprotein (HDL) cholesterol levels <40 mg/dL for women or <50 for men were observed in 9 (47%) patients in the RAL group and 11 (55%) individuals in the EFV arm (P = .634). At baseline, median CAP values of both groups were not significantly different. Other metabolic characteristics of the study population are summarized in Table 1.

Virological, Immunological, and Safety Outcomes

Seven patients presented transient blips of viremia (61–1225 copies/mL) during follow-up, 2 (10.5%) in the RAL group

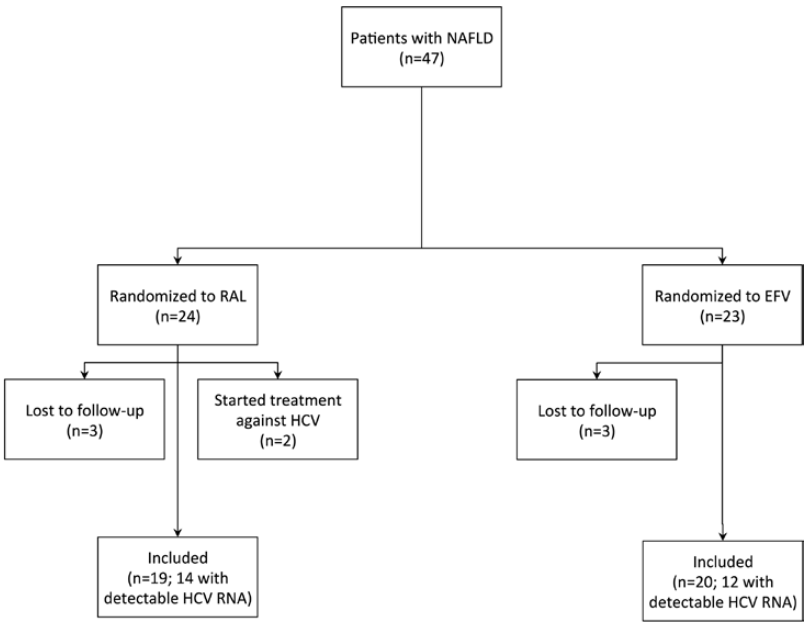

Figure 1. Disposition of the study patients. Abbreviations: EFV, efavirenz; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; RAL, raltegravir.

Table 1. Baseline Characteristics

Characteristic	Raltegravir Group (n = 19)	Efavirenz Group (n = 20)	*P* Value
Age[a], y	52 (45–55)	48 (47–52)	.158
Male sex, No. (%)	17 (90)	15 (80)	.939
CD4 count[a], cells/μL	556 (342–856)	582 (371–774)	.954
CD8 count[a], cells/μL	728 (531–916)	651 (463–952)	.909
Plasma HIV RNA <50 copies/mL, No. (%)	19 (100)	18 (95)	.515
Detectable HCV RNA, No. (%)	14 (74)	12 (68)	.874
BMI[a], kg/m^2	27 (23.9–29.5)	25 (23.7–26.6)	.503
Fasting plasma glucose[a], mg/dL	96 (88–105)	94 (83–110)	.603
HOMA[a]	2.4 (1.8–4)	2.2 (1.8–5.4)	.759
Triglycerides[a], mg/dL	102 (80–136)	117 (88–166)	.977
Total cholesterol[a], mg/dL	173 (133–185)	174 (159–202)	.258
LDL-C[a], mg/dL	83 (63–110)	117 (86–131)	.081
HDL-C[a], mg/dL	50 (42–64)	50 (40–62)	.964
Total cholesterol/HDL ratio[a]	3.2 (2.2–4.5)	3.5 (3.2–4.6)	.380
ALT[a], IU/mL	32 (24–70)	44 (27–77)	.283
AST[a], IU/mL	32 (25–53)	37 (25–65)	.687
GGT[a], IU/mL	73 (57–112)	79 (41–203)	.813
Total bilirubin[a], mg/dL	0.4 (0.3–0.5)	0.41 (0.31–0.6)	.194
Waist circumference[a], cm	89 (84–98)	93 (89–97)	.838
Hip circumference[a], cm	98 (92–103)	95 (93–101)	.708
Waist/hip ratio[a]	0.95 (0.90–1.0)	0.95 (0.91–1.0)	.683
Systolic blood pressure[a], mm Hg	126 (115–134)	119 (110–130)	.633
Diastolic blood pressure[a], mm Hg	80 (66–85)	80 (71–88)	.346
CAP[a], dB/m	273 (246–303)	263 (245–294)	.607
Liver stiffness[a], kPa	7.6 (5.3–10.9)	6.3 (3.8–9.5)	.235
Nucleoside backbone, No. (%)			.407
Tenofovir/emtricitabine	15 (79)	18 (90)	
Abacavir/lamivudine	4 (21)	2 (10)	
Time on efavirenz before randomization[a], mo	93 (76–132)	113 (79–151)	.771

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; GGT, γ-glutamyltranspeptidase; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; HOMA, homeostatic model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol.

[a]Median (Q1–Q3).

and 5 (25%) in the EFV group. There were no persistent viral rebounds. CD4 and CD8 cell counts did not change significantly between baseline and week 48 within each group. At week 48, CD4 cell counts were 628 (401–755) cells/μL in the RAL group and 553 (317–766) cells/μL in the EFV group (P = .422).

No patients discontinued therapy because of adverse events. Four patients showed clinical adverse events during follow-up. Two patients on RAL plus ABC/3TC complained of gastrointestinal symptoms, such as vomiting and diarrhea, self-limited and regarded as mild. One patient on EFV plus ABC/3TC had insomnia and vivid dreams considered as mild. Among laboratory adverse events, 2 patients in the RAL group with elevated baseline alanine or aspartate aminotransferase levels showed grade 2 aminotransferase elevations between week 12 and week 24. These elevations were not related with alcohol use. All women reported a daily alcohol intake <40 g. One (5.3%) man in the RAL group and 1 (5%) in the EFV group reported an alcohol intake >50 g/day.

Changes in Controlled Attenuation Parameter Values

At baseline, the median CAP values were 273 (Q1–Q3, 246–303) dB/m for the RAL group and 263 (Q1–Q3, 245–294) dB/m for the EFV group (P = .607). At week 48, the median CAP for patients switching to RAL was 250 (Q1–Q3, 221–277) dB/m and 286 (Q1–Q3, 269–314) dB/m for those continuing on EFV (P = .035; Figure 2A). The median difference in CAP measurements between baseline and week 48 was –20 (Q1–Q3, –67 to 15) dB/m among individuals in the RAL arm and 30 (Q1–Q3, –17 to 49) dB/m for patients in the EFV group (P = .011; Figure 2B). CAP values <238 dB/m, indicative of absence of significant hepatic steatosis, were observed in 9 (47%) patients in the RAL group and 3 (15%) individuals in the EFV group at week 48 (P = .029).

After excluding patients with ABC/3TC backbone, the median CAP after 48 weeks of follow-up for patients starting RAL was 237 (Q1–Q3, 221–274) dB/m and 286 (Q1–Q3, 267–315) dB/m for those continuing on EFV (P = .025). The median difference in CAP values between baseline and week 48 was –23 (Q1–Q3, –74 to 8) dB/m among individuals in the RAL arm

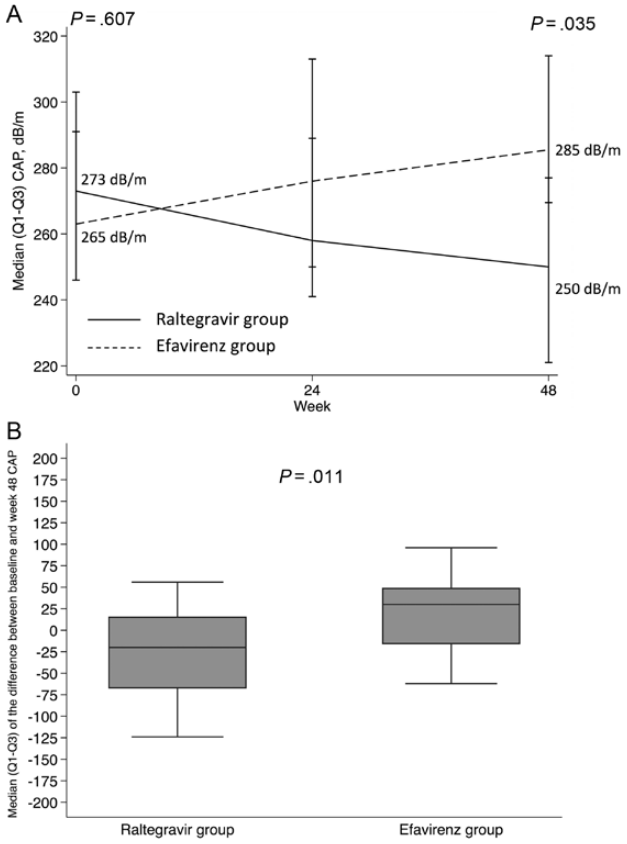

Figure 2. *A*, Median (Q1–Q3) controlled attenuation parameter (CAP) values by treatment group during follow-up (solid lines, raltegravir group; dashed lines, efavirenz group). *P* values show comparisons between treatment groups. *B*, Comparison of median changes in CAP values. Boxplots represent the median of the difference in CAP value between baseline and week 48.

and 30 (Q1–Q3, –19 to 48) dB/m for patients in the EFV group ($P = .006$).

Median liver stiffness at week 48 was 6.3 (Q1–Q3, 5.6–12) kPa for the RAL group and 5.9 (Q1–Q3, 4.5–9.3) kPa for the EFV group ($P = .550$). The median of the change in liver stiffness between baseline and week 48 was –0.3 (Q1–Q3, –1.9 to 1.7) kPa for patients in the RAL arm and 0.05 (Q1–Q3, –0.78 to 2.1) kPa for individuals in the EFV arm ($P = .351$).

In an analysis restricted to the 26 patients with detectable HCV RNA, the baseline median CAP values were 277 (Q1–Q3, 242–305) dB/m for the RAL group and 262 (Q1–Q3, 245–285) dB/m for the EFV group ($P = .432$). At week 48, the median CAP was 266 (Q1–Q3, 221–301) dB/m for patients switching to RAL and 285 (Q1–Q3, 270–316) dB/m for those continuing on EFV ($P = .118$). The median difference in CAP measurements between baseline and week 48 was –7 (Q1–Q3, –67 to 26) dB/m among individuals in the RAL arm and 30 (Q1–Q3, –3.5 to 49) dB/m for patients in the EFV group ($P = .019$). CAP values <238 dB/m, indicative of absence of significant hepatic steatosis, were observed in 5 (36%) patients in the RAL group and 1 (8.3%) individuals in the EFV group at week 48 ($P = .099$).

Metabolic Parameters and Controlled Attenuation Parameter Changes

At week 48, the median BMI for individuals switched to RAL compared with those continuing on EFV was 27.6 (Q1–Q3, 24.3–31) kg/m^2 vs 25.5 (Q1–Q3, 23.8–29.9) kg/m^2 ($P = .084$). Weight increase from baseline to week 48 was a median of 1.2 (Q1–Q3, –2.0 to 6.2) kg in patients on RAL and 0.5 (Q1–Q3, –1.5 to 2.5) kg in those on EFV ($P = .284$). The median waist-to-hip ratio was 0.97 (Q1–Q3, 0.91–1.0) for patients in the RAL group and 0.95 (Q1–Q3, 0.9–1) for those in the EFV group at week 48 ($P = .682$). Among individuals without lipid-lowering drugs, total cholesterol and triglycerides showed greater decreases from baseline among patients switched to RAL (Table 2).

At week 48, the median CAP of patients with and without increases in BMI ≥0.5 kg/m^2 was 282 (Q1–Q3, 267–316) dB/m and 237 (Q1–Q3, 213–292) dB/m, respectively ($P = .013$). Individuals with BMI increase experienced a median CAP raise of 27 (Q1–Q3, –8.5 to 44) dB/m compared with –33 (Q1–Q3, –71 to 21) dB/m for those without BMI increase ($P = .014$). Among patients not exposed to lipid-lowering drugs, those with any decrease in triglyceride levels between baseline and week 48 showed a median change in CAP of –79 (Q1–Q3, –112 to 2.8) dB/m, whereas the median difference in CAP values between baseline and week 48 was 26 (Q1–Q3, –18 to 33) dB/m for those with increases in triglyceride levels ($P = .005$).

Table 2. Changes in Lipid Profile Among Patients Without Lipid-Lowering Drugs (n = 33)

	Median (Q1–Q3) Concentration at Week 48		Median (Q1–Q3) Change in Concentration Between Baseline and Week 48		
Lipid	Raltegravir Group	Efavirenz Group	Raltegravir Group	Efavirenz Group	*P* Value[a]
Triglycerides, mg/dL	107 (79–159)	125 (97–238)	–9 (–33 to 19)	24 (–4.3 to 74)	.010
TC, mg/dL	162 (115–182)	172 (162–192)	–18 (–25 to 6.5)	0.5 (–17 to 10)	.094
LDL-C, mg/dL	88 (61–110)	102 (82–127)	–4 (–12 to 4.5)	–1.0 (–8.8 to 12.5)	.488
HDL-C, mg/dL	42 (33–54)	50 (43–55)	–8 (–13 to –3)	–4.5 (–9 to –1.3)	.191
TC/HDL ratio	3.2 (2.6–4.9)	3.8 (3.2–4.5)	0.3 (–0.04 to 0.7)	0.2 (–0.1 to 0.6)	.958

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

[a] *P* values for the difference in change from baseline to week 48 between treatment groups.

DISCUSSION

After 48 weeks, HIV-infected individuals with NAFLD switched from an EFV- to a RAL-based combination showed a decrease in the degree of hepatic steatosis, as measured by CAP, compared with those continuing with an EFV-based regimen. In addition, the proportion of patients showing regression in significant hepatic steatosis after 48 weeks was greater in those who switched from EFV to RAL.

The difference in outcomes in this trial was due to both increases in CAP levels in the EFV group and decreases in CAP values in the RAL arm. In vitro data indicate that EFV can induce hepatic steatosis [13]. In a prior study conducted in HIV/HCV-coinfected patients, progression of hepatic steatosis was related to cumulative exposure to EFV [8], so that the longer the time on EFV, the higher the frequency of patients with fatty liver progression, a behavior similar to the effect of dideoxynucleosides on hepatic steatosis [8]. However, in the above-mentioned study, the effect of EFV on hepatic steatosis progression could have been confounded by dideoxynucleoside concomitant use. Here we found that EFV plus the nucleoside analogues currently used, TDF/FTC or ABC/3TC, led to elevations in values of CAP with time. Concerning RAL, conversely to EFV, it does not alter the mitochondrial function of hepatic cells in vitro [14]. In addition, RAL was associated with a trend to lower frequency of fatty liver measured by CAP in a cross-sectional study, similar to other metabolic-friendly drugs such as maraviroc or nevirapine [3]. In a longitudinal study, patients using RAL during a 12-month period of observation showed a significant decrease in CAP measurements [21]. However, these observational data were subject to selection bias in patients with RAL, due to previous metabolic toxicities or concomitant combination of RAL with ritonavir-boosted protease inhibitors. In this controlled clinical trial, where this bias is eliminated, we found that RAL can prevent the progression of hepatic steatosis and even decrease the frequency of fatty liver determined by CAP.

The reduction in CAP values and hence the lower rate of significant hepatic steatosis in patients switched from EFV to RAL may be explained by different mechanisms. First, the more friendly metabolic profile of RAL might have contributed to reversal of fatty liver. In this regard, patients starting TDF/FTC plus RAL show fewer increases in the blood levels of low-density lipoprotein cholesterol, total cholesterol-to-HDL ratio, and triglycerides than individuals starting TDF/FTC plus EFV [16, 17]. Similarly, switching from a boosted-ritonavir protease inhibitor–based regimen to RAL-containing combinations is associated with improvements in the lipid profile [18, 19, 24]. Substitution of EFV by RAL had also a significant and favorable impact on lipid levels in a prior trial [20]. Similar changes in the lipid profile were found in the present study, with a greater effect on triglycerides. In addition, triglyceride level decreases between baseline and week 48 were associated with reductions in CAP values in the herein-reported trial. Second, the discontinuation of EFV itself may also have contributed to the decrease in CAP values. EFV could induce hepatic steatosis through mitochondrial toxicity [25]. In cell cultures of human adipocytes, EFV impairs the morphological adipogenic differentiation and adipogenic gene expression in a dose-dependent fashion [26]. This in vitro effect could account for the increased risk of lipodystrophy associated with EFV, and it may also be involved in hepatic steatosis. In this regard, EFV enhances fatty accumulation in hepatocyte cell lines in vitro [13, 14]. In the herein-reported trial, patients continuing on EFV showed increasing CAP measurements. In this way, lack of mitochondrial damage induced by RAL could have allowed the reductions in CAP values after stopping the mitochondrial toxicity of EFV.

In a recent survey evaluating the prevalence of significant hepatic steatosis using CAP among HIV-infected patients, metabolic factors were the strongest predictors of fatty liver [3]. Hepatic steatosis was less likely among those exposed to RAL, maraviroc, or nevirapine [3]. However, BMI was the only independent predictor of significant hepatic steatosis in the multivariate analysis. In a Canadian cross-sectional study, BMI was also the strongest predictor of significant hepatic steatosis as measured by CAP [4]. Similar findings were observed in a longitudinal study on short-term changes in hepatic steatosis measured by CAP [21]. Thus, increases in BMI were the only independent factor related with rise in CAP values. In the present trial, BMI and CAP measurements paralleled; that is, increases in BMI during the follow-up were related with higher CAP values at week 48. Patients who switched to RAL showed greater BMI, close to statistical significance, than those continuing with EFV at week 48. In spite of this and the correlation between BMI and CAP, individuals randomized to replace EFV by RAL presented lower CAP values at week 48. This finding suggests that the effects of EFV substitution by RAL on fatty liver could be independent of BMI, and related with both the interruption of a drug with mitochondrial toxicity and the favorable metabolic profile of RAL. It is not known whether the effect on hepatic steatosis of switching EFV by RAL might also be observed with other HIV integrase inhibitors. If improvements in fatty liver after discontinuing EFV were related with stopping EFV toxicity, then switching to another HIV integrase inhibitor could lead to reductions in hepatic steatosis similar to those obtained in the present trial, provided that switching to other HIV integrase inhibitors was followed by similar effects of the lipid profile as those seen after switching to RAL.

This clinical trial was initially designed to evaluate changes in CAP values among patients with active HCV infection. The availability of highly efficacious all-oral treatment against HCV meant that most HIV/HCV-coinfected patients were eligible for anti-HCV therapy and, thus, not candidates for the trial. As a consequence, a major amendment was introduced to allow the inclusion of patients without active HCV coinfection. In spite of this, individuals with detectable plasma HCV

RNA represented more than two-thirds of the study population. Because factors associated with hepatic steatosis among HIV-infected patients with and without HCV coinfection were similar [3, 21], we expected comparable fatty liver changes after switching EFV by RAL in HIV-infected patients with and without active HCV infection. In the present study, an analysis of CAP changes restricted to patients with detectable plasma HCV RNA yielded similar results to the overall population analysis. Thus, it is highly likely that the results reported herein can be generalized to HIV-infected patients without HCV coinfection.

This study may have some limitations. First, the trial was interrupted before reaching the planned sample size. However, in an intermediate analysis the difference in CAP values at week 48 between groups was larger than the initial estimation. This allowed us to detect a statistically significant difference in CAP values between groups at week 48 with a smaller sample size. Nevertheless, these trial results should be regarded as exploratory and preliminary. Second, we used CAP instead liver biopsy, which can be considered the gold standard for the diagnosis of NAFLD. However, the use of CAP to grade hepatic steatosis has been validated in different populations using liver biopsy as reference [23, 27–31]. The CAP cutoff value of 238 dB/m exhibits high positive and negative predictive values for significant hepatic steatosis [23], and this cutoff has been validated in a prospective study [27]. In addition, studies evaluating switching antiretroviral drugs with repeated determinations of hepatic steatosis among HIV-infected patients might not be feasible using an invasive technique such as liver biopsy. Third, CAP allowed us to evaluate changes in fatty liver, but steatohepatitis cannot be ascertained using CAP. Given that progression of fibrosis and the emergence of cirrhosis seem tightly linked with steatohepatitis, further studies evaluating the influence of antiretroviral drugs on steatohepatitis as end-point are needed.

In conclusion, replacement of EFV by RAL among individuals with significant hepatic steatosis led to reductions in the grade of hepatic steatosis, even reversal of fatty liver in some cases, after 48 weeks. This effect may be related to the discontinuation of EFV and its potential mitochondrial toxicity, plus the metabolic-friendly properties of RAL. These results need confirmation in a larger study, also including drugs commonly used currently (eg, dolutegravir, elvitegravir, and protease inhibitors). Finally, studies using noninvasive diagnostic tools that enable the accurate identification of steatohepatitis are also desirable.

Notes

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