Effects of Switching From Efavirenz to Raltegravir on Endothelial Function, Bone Mineral Metabolism, Inflammation, and Renal Function: A Randomized, Controlled Trial

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Abstract: We performed a randomized controlled trial in 30 HIV-infected participants to either continue tenofovir/emtricitabine/efavirenz (Continuation Group) or switch to tenofovir/emtricitabine/raltegravir (Switch Group) for 24 weeks. There were no significant differences in the changes in flow-mediated dilation, 25(OH) vitamin D, or parathyroid hormone levels. Total cholesterol, high sensitivity C-reactive protein, serum alkaline phosphatase, sCD14 levels, and renal function significantly declined in the Switch Group compared with the Continuation Group; however, sCD163 levels significantly increased in the Switch Group. These findings suggest that raltegravir is not inherently more beneficial to endothelial function compared with efavirenz but may impact renal function and monocyte activation.

Key Words: efavirenz, raltegravir, endothelial function, vitamin D, monocyte activation, renal function

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INTRODUCTION

As HIV-infected patients are achieving nearly normal life expectancies with the use of potent antiretroviral therapies (ARTs), cardiovascular disease (CVD) has emerged as a leading cause of morbidity and mortality.[1] One mechanism by which HIV infection or its therapies may lead to this increased risk in CVD is through impairment of the vascular endothelium. We recently completed a 12-month observational study in which we assessed flow-mediated dilation (FMD), a measure of in vivo endothelial function, for 12 months in HIV-infected patients initiating their first ART regimen.[2] Although FMD did not significantly change in the entire group, we observed worsening FMD with efavirenz (EFV)-based treatment and an improvement in FMD in those receiving protease inhibitors. The large reduction in FMD in the EFV group was primarily in those receiving the combination of tenofovir (TDF), emtricitabine (FTC), and EFV. Another recent study also suggested that the initiation of EFV-based regimens, most of which also incorporated TDF, led to a decrease in FMD.[3] Although large observational studies, such as the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, have suggested no increase in risk of myocardial infarctions with use of non–nucleoside reverse transcriptase inhibitors such as EFV,[4] in the randomized trial ACTG 5202, the use of TDF/FTC/EFV was associated with numerically more acute ischemic events compared with other once-daily regimens, including those incorporating abacavir.[5] Taken together, these findings suggest a potentially adverse effect of EFV, especially the combination of TDF/FTC/EFV, on cardiovascular health.

One possible mechanism for an adverse effect of TDF/FTC/EFV on CVD risk may involve the calcium–phosphorus homeostasis axis, with reductions of circulating vitamin D levels with EFV and/or increases in parathyroid hormone levels with TDF, respectively; both abnormalities have been associated with endothelial dysfunction.[6–9] If secondary hyperparathyroidism because of EFV, especially when coupled with TDF, is the cause of increased CVD risk with this specific combination, then perhaps removing the EFV component from an ART regimen would be beneficial. Therefore, we conducted a randomized trial assessing the effects of switching HIV-infected patients receiving TDF/FTC/EFV to TDF/FTC/raltegravir (RAL) on endothelial function and markers of bone mineral metabolism.

METHODS

Study Design

We performed a single-center, open-label, randomized, controlled trial in 30 HIV-infected study participants who had

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been receiving TDF/FTC/EFV as their initial HIV treatment regimen (ClinicalTrials.gov; NCT01270802). Participants were randomized 1:1 to continuing treatment with TDF/FTC/EFV ("Continuation Group") versus switching their regimen to TDF/FTC plus RAL 400 mg twice daily ("Switch Group"). Study procedures were performed at entry, week 8, and week 24. Randomization in varying sized blocks (2, 4, or 6) was used for this study. This trial was approved by the Indiana University Institutional Review Board. All participants provided written, informed consent before screening. Merck & Co., Inc. provided both an unrestricted research grant in support of this trial and RAL for those assigned to the Switch Group but had no role in the design, conduct, or reporting of the study results.

Study Population

Participants were recruited from the HIV outpatient clinics associated with the Indiana University Health medical system. Primary inclusion criteria included patients having documented HIV-1 infection, of age 18 years and older, receiving TDF/FTC/EFV as their initial treatment regimen for at least 1 year before screening, and having both an HIV RNA level of <50 copies per millimeter at screening and between 1 and 6 months before screening. Major exclusion criteria included diagnosed CVD, diabetes, uncontrolled hypertension (screening systolic blood pressure >160 mm Hg or diastolic pressure >90 mm Hg), other systemic inflammatory disease (although hepatitis B or C coinfection was allowed); estimated creatinine clearance <50 mL/min; or use of lipid-lowering drugs.

Study Procedures

Participants were required to fast and not smoke for at least 8 hours before all study procedures. FMD and nitroglycerin-mediated dilation studies were performed using an Acuson CV70 ultrasound machine at all study visits according to recommended guidelines[10] by a single registered vascular ultrasonographer. Images were interpreted by a blinded single investigator (S.K.G.) using Access Point Web software (Freeland Systems, Westminster, CO). The intraclass correlations for reproducibility for baseline diameter and FMD measured twice in 12 healthy volunteers in our laboratory under these conditions were 0.97 and 0.73, respectively.

Circulating inflammatory markers [high sensitivity C-reactive protein (hsCRP), serum interleukin-6 (IL-6), soluble tumor necrosis factor-α receptors I and II (sTNFRI and sTNFRII), monocyte chemoattractant protein-1 (MCP-1), interferon-γ-inducible protein-10 (IP-10)], endothelial markers (soluble vascular cell adhesion molecule-1, asymmetric dimethylarginine), markers of monocyte/macrophage activation [soluble CD14 (sCD14), soluble CD163 (sCD163)], and metabolic markers [serum cystatin C, lipid fractions, insulin] were measured at the University of Vermont Laboratory for Clinical Biochemistry Research. Serum calcium, phosphorus, parathyroid hormone (PTH), 25(OH) vitamin D, and fibroblast growth factor-23 (FGF-23) were measured in the research laboratory of 1 investigator (S.M.M.). All these markers were measured in batch from archived frozen samples kept at $-80°C$. Serum glucose, creatinine, and CD4 cell count along with urine albumin, protein, phosphorus, and creatinine levels (measured on fasting morning urine samples) were assessed at the Indiana University Health clinical laboratory. Renal function was estimated as creatinine clearance with the Cockcroft–Gault equation[11] and as glomerular filtration rates (eGFRs) using the 2009 CKD-EPI equation,[12] the 2012 CKD-EPI cystatin C equation,[13] and the 2012 CKD-EPI combined cystatin C-creatinine equation.[13] The homeostasis model assessment-insulin resistance was used to estimate insulin resistance from fasting glucose and insulin measures.[14]

Statistical Analyses

We assumed that the declines in FMD seen with TDF/FTC/EFV in our previous study[2] would fully reverse with switch to TDF/FTC/RAL. Thus, the clinically relevant effect size to be detected for FMD change was +3.12% with a standard deviation of 4% in those switching from EFV to RAL. Using a 2-sample, independent, 2-tailed t test with 5% Type I error and 20% Type II error, a sample size of 13 per group would be needed to find a difference in FMD between groups. Allowing for a 10% dropout rate, we planned to recruit 15 subjects per group.

Categorical variables were examined using Fisher exact test. We employed Student t test for comparisons of continuous measures as we found no evidence of violation of the normality assumption for these variables. Of note, serum glucose, calcium, PTH, 25(OH) vitamin D, FGF-23, hsCRP, IL-6, triglycerides, MCP-1, HIV-1 RNA, homeostasis model assessment-insulin resistance, urine albumin/creatinine, urine protein/creatinine, and urine calcium/creatinine required logarithmic transformation to approximate normal distributions before such analysis. Wilcoxon rank sum tests were also performed for log-transformed variables, and the same significance levels were obtained (data not shown).

Analyses were performed as intention to treat but without corrections for multiple testing for the secondary analyses. Two-sided P values of <0.05 were considered statistically significant. All analyses were performed in SAS 9.3 (SAS Inc., Cary, NC).

RESULTS

Study Cohort Characteristics

Enrollment into this trial occurred between April 2011 and May 2012. Thirty-two persons screened for enrollment. Two of these failed screening for having screening HIV-1 RNA levels of >50 copies per millimeter; the remaining 30 persons were equally randomized into the 2 study groups. Of these, 1 participant in the Continuation Group was removed at entry for confirmed virologic failure (repeat HIV-1 RNA >50 copies/mL). One participant in the Continuation Group withdrew from participation between entry and week 8 because of moving out of area. One participant in the Switch Group was lost to follow up between week 8 and week 24. Thus, 13 and 15 participants were assessed in the

Continuation Group and Switch Group at week 8, respectively, whereas 13 and 14 participants were assessed at week 24 in the 2 groups. Table 1 shows the well-balanced baseline characteristics of the 30 enrolled participants.

Changes in Vascular Measures

The vascular results are shown in Table 2 and in Table S1 (see **Supplemental Digital Content**, http://links.lww.com/QAI/A455, which shows additional secondary data comparisons). There were no significant changes in FMD, asymmetric dimethylarginine, or soluble vascular cell adhesion molecule-1 between the groups at either week 8 or week 24.

Changes in Bone Mineral Markers

There were no significant differences in the changes between groups in PTH, 25(OH) vitamin D, or FGF-23 levels at either week 8 or week 24 (Table 2; see **Table S1, Supplemental Digital Content**, http://links.lww.com/QAI/A455). Alkaline phosphatase levels significantly decreased more in the Switch Group than in the Continuation Group at week 24.

Changes in Metabolic Markers

Total cholesterol levels decreased significantly at both weeks 8 and 24 in the Switch Group compared with the Continuation Group (Table 2). There was also a significant decrease in the Switch Group in LDL-C at week 8, but there no significant differences between groups in LDL-C at week 24.

Changes in Inflammatory Markers

As shown in Table 2, hsCRP levels and sCD14 levels decreased significantly more so in the Switch Group than the Continuation Group at weeks 8 and 24. There was a significant increase in sCD163 in the Switch Group compared with the Continuation Group at week 24. There were no significant differences between groups in the other inflammatory markers (see **Table S1, Supplemental Digital Content**, http://links.lww.com/QAI/A455).

TABLE 1. Baseline Characteristics of the Study Groups

Characteristic	Continuation Group (N = 15)	Switch Group (N = 15)
Age, yrs	38 (12.0)	39 (10.6)
Male sex	13 (87%)	14 (93%)
Black race	8 (53%)	10 (67%)
Hispanic ethnicity	0 (0%)	0 (0%)
Current smoker	8 (53%)	9 (60%)
Active hepatitis B	2 (13%)	2 (13%)
Active hepatitis C	1 (7%)	1 (7%)
Weight, kg	88.2 (17.3)	84.7 (17.9)
Body mass index, kg/m^2	28.2 (5.5)	27.6 (6.3)
Baseline brachial artery diameter, cm	0.43 (0.07)	0.42 (0.04)

Data presented as mean (standard deviation) or numbers (percent); active hepatitis B defined as having a positive surface antigen on record or at screening; active hepatitis C defined as having a positive antibody on record or at screening.

Changes in Renal Function Markers

Interestingly, we found significant decreases in creatinine clearance at week 24 (but not at week 8) and in all 3 GFR estimates in the Switch Group compared with the Continuation Group at week 8 with significant differences in eGFR persisting using just the two 2012 CKD-EPI equations at week 24 (Table 2). However, there were no significant differences between groups in the changes in urine albumin/creatinine or protein/creatinine ratios at either time point.

Safety

There were no safety concerns in this trial apart from the 1 participant in the Continuation Group who was removed after fulfilling virologic failure criteria at entry; there were no virologic failures in the Switch Group. There were no significant differences in numbers or types of adverse events between the Groups. None of these adverse events were treatment limiting.

DISCUSSION

In HIV-infected study participants receiving TDF/FTC/EFV as their first regimen and with suppressed viremia, we did not find that switching the EFV component of this regimen to RAL resulted in changes in endothelial function over 24 weeks. These data do not support the hypothesis that RAL is intrinsically more beneficial to the endothelium compared with EFV. Our results are similar to those found by Masia et al[15] who also found no change in FMD by switching from a protease inhibitor to RAL or by Hatano et al[16] who found no improvement in FMD after RAL intensification.

We had speculated that any potential changes in FMD with switch from EFV to RAL could be because of changes in vitamin D or PTH.[17] However, none of the serum or urine bone mineral markers changed significantly apart from a reduction in serum alkaline phosphatase in the Switch Group as expected.[18]

Total cholesterol levels improved in the Switch Group, which corroborates findings from previous studies assessing switches from protease inhibitors[15,19,20] or EFV[20] to RAL. Similar findings in ART-naive studies comparing RAL to EFV showed less effects of RAL on lipid profiles.[21]

We surprisingly found declines in renal function, both in estimated creatinine clearance and in eGFR, in the Switch Group compared with the Continuation Group. The differences between groups in eGFR we observed were approximately 10 $mL \cdot min^{-1} \cdot 1.73^2$, which are similar to the declines found in those initiating TDF.[5,22,23] The integrase inhibitor dolutegravir has been reported to increase serum creatinine through inhibition of creatinine secretion by means of the human organic cation transporter 2 in the renal proximal tubule but does not lead to actual declines in directly measured GFR.[24] This inhibition of human organic cation

TABLE 2. Comparisons of Changes in Vascular, Metabolic, Inflammatory, Bone, and Renal Markers at Week 8 and Week 24

	Continuation Group			Switch Group		
Laboratory Marker	**Entry**	**8-Week Change**	**24-Week Change**	**Entry**	**8-Week Change**	**24-Week Change**
Vascular markers						
Flow-mediated dilation, %	3.82 (2.71)	−0.41 (2.15)	−0.67 (3.35)	3.09 (2.36)	1.17 (4.20)	−0.10 (3.26)
Nitroglycerin-mediated dilation, %*	17.46 (9.08)	6.88 (9.42)	−0.15 (8.55)	17.85 (8.46)	−3.02 (6.43)	−4.77 (8.95)
Metabolic markers						
HOMA-IR	1.75 (1.31)	−0.04 (1.09)	0.58 (1.18)	1.67 (0.94)	0.17 (1.48)	0.60 (1.42)
Serum total cholesterol, mg/dL*†	156.87 (32.93)	4.00 (16.86)	1.08 (9.88)	154.07 (36.67)	−12.2 (16.95)	12.64 (19.61)
Serum HDL-C, mg/dL	42.27 (10.16)	0.85 (6.62)	0.15 (6.09)	39.33 (11.64)	0.13 (6.48)	0.29 (6.06)
Serum LDL-C, mg/dL*	89.39 (28.93)	6.08 (16.01)	−2.23 (15.13)	90.61 (37.78)	−8.58 (17.14)	−8.65 (18.24)
Serum triglycerides, mg/dL	125 (64)	−13 (36)	16 (98)	120 (77)	−19 (66)	−22 (25)
Immunologic/inflammatory markers						
Serum hsCRP, mg/L†	2.55 (2.45)	0.99 (6.13)	−0.66 (2.07)	3.93 (3.95)	−0.84 (2.70)	−2.16 (2.20)
Serum IL-6, pg/mL	1.95 (1.42)	−0.34 (1.32)	−0.62 (1.10)	1.47 (1.66)	0.24 (1.32)	−0.10 (0.88)
sCD14, ng/mL*†	2441.15 (378.02)	−173.28 (321.51)	−112.54 (421.26)	2443.2 (283.94)	−412.16 (288.84)	−458.14 (319.03)
sCD163, ng/mL†	575.80 (252.64)	−28.96 (60.04)	−32.26 (64.18)	577.21 (183.58)	15.24 (90.31)	32.00 (63.57)
Bone homeostasis markers						
Serum alkaline phosphatase, mg/dL†	84.00 (23.15)	−7.58 (9.85)	−4.92 (8.2)	78.47 (15.25)	−7.07 (7.47)	−12.46 (9.44)
Serum parathyroid hormone, pg/mL	62.41 (18.39)	0.19 (19.04)	11.45 (39.73)	56.51 (27.70)	−5.76 (22.42)	−10.08 (25.64)
Serum 25(OH) vitamin D, ng/mL	18.35 (20.31)	−1.01 (6.70)	−0.58 (9.95)	13.70 (12.86)	5.28 (9.46)	4.50 (12.52)
Renal function/injury markers						
Serum creatinine, mg/dL*‡	0.91 (0.23)	−0.01 (0.06)	−0.02 (0.10)	0.93 (0.16)	0.06 (0.08)	0.08 (0.08)
Serum cystatin C, mg/L‡§	0.80 (0.14)	−0.06 (0.07)	−0.03 (0.06)	0.75 (0.11)	0.07 (0.09)	0.07 (0.1)
Creatinine clearance, mL/min‡	129.64 (41.61)	−2.00 (18.78)	12.25 (23.29)	130.93 (39.88)	−7.36 (14.37)	−11.69 (12.66)
Estimated GFR (2009 CKD-EPI), mL/min/1.73^2§	110.55 (23.73)	0.51 (4.71)	0.74 (9.40)	111.15 (20.89)	−4.77 (9.80)	−8.67 (8.78)
Estimated GFR (2012 CKD-EPI Cystatin), mL/min/1.73^2‡§	110.40 (17.13)	6.86 (11.54)	3.06 (8.07)	115.79 (12.11)	−8.43 (11.26)	−8.50 (11.04)
Estimated GFR (2012 CKD-EPI Cystatin-Creatinine), mL/min/1.73^2‡§	100.19 (20.38)	5.24 (7.15)	2.72 (6.48)	102.7 (16.78)	−7.09 (9.22)	−8.22 (6.70)
Urine albumin/creatinine, mg/g	7.32 (7.39)	0.86 (8.13)	−1.57 (2.90)	4.84 (3.98)	−1.51 (2.26)	11.99 (44.84)
Urine protein/creatinine, g/g	0.12 (0.07)	−0.01 (0.02)	−0.01 (0.03)	0.08 (0.05)	−0.01 (0.02)	0.01 (0.04)

Data presented as mean (standard deviation).

HOMA-IR, homeostasis model assessment–insulin resistance; HDL-C, high density lipoprotein–cholesterol; LDL-C, low-density lipoprotein–cholesterol; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6; sCD14 and 163, soluble cluster of differentiation 14 and 163; GFR, glomerular filtration rate.

*$P < 0.05$ for differences between groups in the change from entry to week 8.

†$P < 0.05$ for differences between groups in the change from entry to week 24.

‡$P < 0.01$ for differences between groups in the change from entry to week 24.

§$P < 0.01$ for differences between groups in the change from entry to week 8.

transporter 2 should not lead to changes in serum cystatin C. As such, the increases in both cystatin C and creatinine with RAL in this study may suggest a true negative effect on glomerular function. The mechanism by which RAL may worsen renal function in those who are virologically suppressed is not clear. RAL decreases circulating TDF concentrations, so a drug interaction leading to TDF nephrotoxicity is unlikely. In addition, blood pressures did not change significantly between the groups (data not shown).

Regarding the inflammatory markers assessed in this study, hsCRP levels significantly decreased with switch to RAL compared with continuation with EFV, which is in contrast to the findings by Lake et al[20] who found no change in hsCRP in their trial of protease inhibitor switch to RAL among women with central obesity. We also explored potential changes in sCD14 and sCD163 as markers of monocyte activation with switch to RAL. Greater sCD14 levels have been linked to an increased risk of death,[25] whereas higher sCD163 levels have been associated with worsening inflammatory atherosclerotic disease in those with HIV infection.[26,27] Similar to our results, a greater reduction in sCD14 with TDF/FTC/RAL compared with non–RAL-based regimens has been previously reported in ART-naive patients.[28] It is possible that the increased penetration of RAL into gut tissue[29] may lead to decreased viral replication in this reservoir with consequent reductions in bacterial translocation and the monocyte-secreted lipopolysaccharide receptor sCD14. Similar to sCD14, circulating sCD163 levels are increased by lipopolysaccharide and other inflammatory triggers,[30] so it is not clear why switching from EFV to RAL would lead to an apparently paradoxical increase in sCD163.

Limitations to our study should be acknowledged. This study design was open-label as a blinded study with matching placebos was considered too difficult to implement given the

differences in dosing schedules between EFV and RAL. We believe this limitation was somewhat mitigated as the vascular ultrasound readings were blinded. We also acknowledge that the sample size was small, although it was based on our previously published data for the primary endpoint of change in FMD. It is unlikely that we would have found clinically meaningful differences between groups in change in FMD with larger sizes given the minor changes observed. Although the reproducibility of FMD in our laboratory seems modest, the technique in our hands actually compares quite favorably, or even better than, those of other groups.[31,32] Of note, the high variability of FMD was accounted for in our sample size estimate and, as such, likely would not have led to the negative findings. We do acknowledge that it is certainly possible that the study duration was too short to detect changes in FMD and in several biomarkers. We also performed numerous statistical tests without adjustment for these multiple comparisons, so we caution that some significant differences, especially in regards to the differential findings related to the monocyte activation markers, may have been found by chance. However, the reductions in renal function with RAL were found using 2 different markers, namely creatinine and cystatin C, and thus this finding is more likely to be true. Overall, our results should be considered hypothesis-generating with additional research required to determine the mechanisms underlying the potentially negative effects of RAL on renal function along with the long-term benefits and risks of using raltegravir-based regimens.

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