MAJOR ARTICLE

Differential Reduction in Monocyte Activation and Vascular Inflammation With Integrase Inhibitor–Based Initial Antiretroviral Therapy Among HIV-Infected Individuals

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(See the editorial commentary by Erlandson and Campbell on pages 339–42.)

Background. Little is known about how different antiretrovirals effect inflammation and monocyte activation in human immunodeficiency virus (HIV) infection.

Methods. We examined plasma specimens obtained during a randomized, double-blinded trial in antiretroviral therapy (ART)–naive HIV-infected adults which compared the efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/c/FTC/TDF) with that of efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF). From a random sample achieving an HIV type 1 RNA load of <50 copies/mL by week 48, changes over 24 and 48 weeks in levels of biomarkers of monocyte activation (soluble CD14 [sCD14] and soluble CD163 [sCD163]), systemic inflammation (soluble tumor necrosis factor α receptor I [sTNF-RI], interleukin 6 [IL-6], and high-sensitivity C-reactive protein [hsCRP]), and vascular inflammation (lipoprotein-associated phospholipase A_2 [Lp-PLA_2]) were compared. Multivariable linear regression was used.

Results. A total of 200 participants were included. Significant differences favoring EVG/c/FTC/TDF were noted for changes in sCD14, hsCRP, and Lp-PLA_2 levels. Factors independently associated with a larger decrease in the sCD14 level included random assignment to receive EVG/c/FTC/TDF, higher baseline sCD14 level, and larger decreases in hsCRP and sCD163 levels; factors associated with a larger Lp-PLA_2 decrease included higher baseline Lp-PLA_2 and IL-6 levels, smaller increases in total cholesterol and triglycerides levels, a larger decrease in the sCD14 level, and a smaller decrease in the sCD163 level.

Conclusions. EVG/c/FTC/TDF led to greater decreases in sCD14, hsCRP, and Lp-PLA_2 levels, compared with EFV/FTC/TDF. Randomization group independently predicted the change in sCD14 level, and changes in monocyte activation independently predicted the change in Lp-PLA_2 level. There appears to be a more favorable effect of the integrase inhibitor EVG over efavirenz on immune activation, which may affect vascular inflammation.

Keywords. monocyte activation; vascular inflammation; systemic inflammation; antiretroviral-naive; HIV infection.

Advances in antiretroviral therapy (ART) have had an impressive impact on morbidity and mortality due to human immunodeficiency virus (HIV) infection over the last 2 decades, such that life expectancy nears that of the general population in developed countries [1]. As AIDS-related mortality has fallen, the proportion of deaths due to cardiovascular disease (CVD) has increased [2]. Further, it has been shown that HIV-infected patients are at increased risk of myocardial infarction [3, 4] and stroke [5] and that CVD risk during HIV infection may accelerate faster with age than in the general population [6].

While traditional CVD-associated risk factors [7] and ART use [8] have been implicated in the risk of CVD

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among HIV-infected individuals, the role of persistent immune activation, specifically monocyte activation, has recently received much attention, as well [9–11]. Continued immune activation in HIV-infected persons during ART may be the result of enterocyte damage leading to microbial translocation [12, 13], coinfections [14–16], persistent low-level viral replication [17], or ART itself [18], and little is known about the differential effects of the many available antiretroviral medications on inflammation and immune activation in HIV infection. It is plausible that the integrase inhibitor class may decrease inflammation and immune activation more than other antiretroviral classes, because integrase inhibitors are more lipid friendly [19, 20] and may concentrate better in enterocytes [21]. Understanding the effect of specific antiretroviral medications on inflammation is important because there many medications available for the treatment of HIV infection and because inflammation has been linked to mortality in treated infection [22, 23].

The aim of this study was to compare changes from baseline to 24 and 48 weeks in levels of markers of monocyte activation and of systemic and vascular inflammation between ART-naive HIV-infected adults randomly assigned to receive an integrase inhibitor–based regimen, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/c/FTC/TDF) or efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF), in the Gilead 102 study [24]. Our hypothesis was that the markers of monocyte activation and systemic and vascular inflammation would decrease to a greater degree in the EVG/c/FTC/TDF group.

METHODS

Gilead 102 is a 96-week, randomized, double-blinded, active-controlled clinical trial to evaluate the safety and efficacy of EVG/c/FTC/TDF versus that of EFV/FTC/TDF in HIV-infected ART-naive adults. The entry criteria for this study have been published previously [24]. In brief, eligibility criteria were age ≥18 years, HIV-1 RNA level of ≥5000 copies/mL, no prior ART use, genotypic susceptibility to emtricitabine, tenofovir, and efavirenz, estimated glomerular filtration rate (eGFR) of ≥70 mL/min by the Cockcroft-Gault equation, liver transaminase levels ≤5 times the upper limit of normal, absolute neutrophil count of ≥1000 neutrophils/mm^3, platelet count of ≥50 000 platelets/mm^3, hemoglobin level of ≥8.5 g/dL, life expectancy of ≥1 year from the time of enrollment, no AIDS-defining conditions diagnosed within 30 days, not currently receiving treatment for hepatitis C or other drugs known to interact with the study medications or systemic corticosteroids, no active infection or malignancy, and no current alcohol or substance use judged to potentially interfere with study compliance. Participants were randomly assigned at a ratio of 1:1 to receive EVG/c/FTC/TDF or EFV/FTC/TDF, as well as placebo matching the study drug administered to the other treatment group. The participants for this study were a random sample of Gilead 102 participants who achieved an HIV-1 RNA level of <50 copies/mL by week 48 and had a stored plasma specimen available from entry, week 24, and week 48 visits. All participants of the Gilead 102 study provided written informed consent, which included consent for use of stored blood specimens for clinical tests to be performed later. This study was approved by the University Hospitals Case Medical Center Institutional Review Board.

The primary outcomes in this study were changes from baseline to week 48 in levels of soluble CD14 (sCD14) and soluble CD163 (sCD163), markers of monocyte activation; levels of soluble tumor necrosis factor α receptor I (sTNF-RI), interleukin 6 (IL-6), and high sensitivity C-reactive protein (hsCRP), markers of systemic inflammation; and the level of lipoprotein-associated phospholipase A_2 (Lp-PLA_2), a marker of vascular inflammation. Secondary outcomes of interest were changes in levels of these markers from baseline to 24 weeks and relationships between changes in monocyte activation and inflammation markers.

Markers of Inflammation and Immune Activation

Participants had blood specimens collected after an 8-hour fast at entry, week 24, and week 48. Plasma specimens were stored at −80°C and never thawed until analysis. Stored plasma samples were analyzed using specific enzyme-linked immunosorbent assay kits as per the manufacturers' instructions (diaDexus [South San Francisco, California] for Lp-PLA_2; R&D Systems [Minneapolis, Minnesota] for all others). Markers with compelling data linking them to CVD risk and mortality during HIV infection were selected [25–29].

Statistical Analysis

Data on demographic characteristics, clinical indices, and HIV-related factors are presented overall and by group at baseline. Median values and interquartile ranges (IQRs) are reported for continuous variables, and numbers and percentages are reported for categorical variables. Absolute and percentage changes from baseline to week 24 and from baseline to week 48 in levels of markers of monocyte activation and inflammation, as well as clinically relevant variables, were determined. All baseline variables and end points were compared between groups, using unpaired *t* tests or Wilcoxon rank sum tests, as warranted by the distribution of data, for continuous variables and using χ^2 tests, Fisher exact tests, or Pearson exact χ^2 tests, as appropriate, for categorical variables. Within-group changes were tested using paired *t* tests or Wilcoxon signed rank tests appropriate for the distribution of data.

For the regression analyses, all variables with nonnormally distributed data were log-transformed prior to model fitting. Univariable followed by multivariable linear regression was used to explore relationships of baseline factors with baseline log-transformed sCD14 and log-transformed Lp-PLA_2. Variables tested in the univariable analyses included age, sex, race,

hepatitis B and C status, weight, $CD4^+$ T-cell count, HIV-1 RNA level, eGFR, hemoglobin level, glucose level, lipoprotein levels, and markers of monocyte activation and inflammation at baseline. All variables with a P value of < .25 in univariable analyses were considered for inclusion in the multivariable model, and backward elimination was used for model selection. Next, 2 separate analyses were performed in which change in sCD14 and Lp-PLA_2 levels were the outcomes. First, analysis of covariance was used to adjust the mean percentage change from baseline to week 48 in log-transformed sCD14 and Lp-PLA_2 levels for baseline levels of these 2 markers and for percentage changes from baseline to week 48 in clinically relevant variables, including weight, $CD4^+$ T-cell count, hemoglobin level, eGFR, glucose level, and lipoprotein levels, with each variable on the same scale as the outcome variable. Last, univariable followed by multivariable linear regression was used to explore predictors of percentage change from baseline to week 48 in log-transformed sCD14 and Lp-PLA_2 levels. Variables tested in the univariable analyses for models with percentage change from baseline to week 48 in log-transformed sCD14 or Lp-PLA_2 levels as the outcome included all baseline variables listed above, as well as percentage change from baseline to week 48 in weight, $CD4^+$ T-cell count, hemoglobin level, eGFR, glucose level, lipoprotein levels, and other markers of monocyte activation and inflammation, with each variable on the same scale as the outcome variable. All final models were checked to be sure the assumptions of linear regression were met.

All statistical tests were 2 sided, and differences with a P value of < .05 were considered statistically significant. Adjustments were not made in this significance level for multiple comparisons. Analyses were performed using SAS, version 9.2 (SAS Institute, Cary, North Carolina).

With 200 participants in this study and the assumption of a conservative common SD of 10%, our study had 80% power to detect a between-group difference as low as 4% in the percentage change in biomarker levels over 48 weeks, using an unpaired t test with a 2-sided 0.05 level of significance.

RESULTS

Baseline Characteristics

Two hundred participants were included in this study (100 in each group). Participants did not differ from the Gilead 102 population with regard to baseline characteristics (data not shown). At baseline, the 2 treatment groups were balanced with regard to all demographic and HIV-related factors, except there were more participants receiving antihypertensive medications in the EVG/c/FTC/TDF group (18% vs 8%; $P = .04$). When comparing individual classes of antihypertensive medications, only diuretic use was higher in the EVG/c/FTC/TDF group (13% vs 3%; $P < .01$); proportion of participants receiving medications from other classes were similar between groups (Table 1). Overall, the median age was 38 years (IQR, 30–44.5 years), and the majority of participants were men (89%) and white (65%); 30% were African American, and 5% were from other racial groups. The median baseline weight was 81 kg (IQR, 70.5–92.6 kg), and the median eGFR was 120.2 mL/min (IQR, 99.2–137.2 mL/min). Three and five participants had chronic hepatitis B virus and chronic hepatitis C virus infections, respectively. All participants were ART naive at study entry, by design, with a median baseline $CD4^+$ T-cell count of 371.5 cell/mm^3 (IQR, 267.5–484.5 cell/mm^3) and a median HIV-1 RNA load of 64 900 copies/mL (IQR, 25 050–147 000 copies/mL). At baseline, 10% were receiving at least 1 cholesterol-lowering medication, including 4 participants receiving an HMG-CoA reductase inhibitor or statin.

Changes in Markers After ART Initiation

At baseline, levels of markers of monocyte activation and systemic and vascular inflammation were similar between groups. Baseline, week 24, week 48 values and absolute changes from baseline to week 24 and to week 48 in levels of all markers are shown in Table 2. Within the EVG/c/FTC/TDF group, levels of all markers decreased significantly relative to baseline by week 48, with the exception of Lp-PLA_2, for which the decrease neared significance ($P = .06$). In the EFV/FTC/TDF group, the changes were mixed. Over 48 weeks, levels of sCD163, sTNF-RI, and IL-6 decreased significantly; however, the level of Lp-PLA_2 increased, and the levels of sCD14 and hsCRP did not change significantly. Percentage changes in the markers are shown in Figure 1. Within-group percentage changes in levels of the markers were similar to the absolute changes except, within the EVG/c/FTC/TDF group, the change in hsCRP level was not statistically significant and, in the EFV/FTC/TDF group, increases in sCD14 and hsCRP levels were significant at both week 24 and week 48. Absolute and percentage changes from baseline to week 24 and from baseline to week 48 were significantly different for sCD14, hsCRP (absolute change only), and Lp-PLA_2 levels, with changes favoring the EVG/c/FTC/TDF group. Changes were similar between groups for sCD163, sTNF-RI, and IL-6 levels. After adjustment for percentage changes from baseline to week 48 in weight, $CD4^+$ T-cell count, hemoglobin level, eGFR, glucose level, and lipoprotein levels, percentage changes from baseline to week 48 in sCD14 and Lp-PLA_2 levels remained significantly different between groups, with changes favoring EVG/c/FTC/TDF (data not shown).

Changes in Other Clinically Relevant Factors After ART Initiation

In this sample, absolute changes in $CD4^+$ T-cell count from baseline to week 24 and from baseline to week 48 were similar between groups (185 cells/mm^3 for EVG/c/FTC/TDF vs 155 cells/mm^3 for EFV/FTC/TDF [$P = .24$] and 246 cells/mm^3 for EVG/c/FTC/TDF vs 217 cells/mm^3 for EFV/FTC/TDF

Table 1. Baseline Demographic, Clinical, and Human Immunodeficiency Virus (HIV)-Related Indices, by Randomization Group

Characteristic	EVG/c/FTC/TDF (n = 100)	EFV/FTC/TDF (n = 100)	*P* Values
Age, y	37 (30.5–44.5)	38 (30–44.5)	.98
Male sex	88 (88)	90 (90)	.65
Race			.69
White	62 (62)	67 (67)	
African American	33 (33)	26 (26)	
Other	5 (5)	7 (7)	
Chronic hepatitis B	0 (0)	3 (3)	.25
Chronic hepatitis C	2 (2)	3 (3)	>.99
Weight, kg	80.7 (69.6–89.8)	81.2 (71.5–95.3)	.37
eGFR, mL/min	116.3 (97.8–139.4)	121.5 (101.1–135.6)	.58
Hemoglobin level, g/dL	14.2 (12.9–15.1)	14.3 (13.5–14.9)	.49
Glucose level, mg/dL	92 (86–98)	91 (84–97)	.37
Cholesterol level, mg/dL			
Total	161.5 (139–181)	161.5 (141–185)	.72
Low-density lipoprotein	98 (79.5–118)	94.5 (82–115)	.9
High-density lipoprotein	41 (35–48)	40 (33–47)	.28
Triglycerides level	98 (79.5–118)	100.5 (78–152)	.39
Antihypertensive medication			
Any[a]	18 (18)	8 (8)	.04
Class			
Renin-angiotensin system agent	12 (12)	8 (8)	.35
β-blocker	3 (3)	0 (0)	.08
Calcium channel blocker	2 (2)	2 (2)	>.99
Diuretic	13 (13)	3 (3)	<.01
Cholesterol-lowering medication			
Any[a]	11 (11)	9 (9)	.64
Class			
Statin	2 (2)	2 (2)	>.99
Fish oil	8 (8)	7 (7)	.79
Fibrate	2 (2)	0 (0)	.16
$CD4^+$ T-cell count, cells/mm^3	369 (279.5–473)	380.5 (249–492)	.96
HIV type 1 RNA level, copies/mL	52 850 (19 550–144 000)	79 300 (36 750–150 500)	.08

Data are median value (interquartile range) or no. (%) of patients.

Abbreviations: EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; eGFR, estimated glomerular filtration rate; EVG/c/FTC/TDF, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.

[a] Defined as use of ≥1 medication.

[*P* = .23], respectively), as was the proportion of participants achieving an HIV-1 RNA level of <50 copies/mL by week 24 (95% and 96% for EVG/c/FTC/TDF and EFV/FTC/TDF, respectively; *P* = .72). By design, all participants had an undetectable HIV-1 RNA level by week 48. The decline in eGFR was greater in the EVG/c/FTC/TDF group, and this was apparent by week 24 (−11.3 and −0.2 mL/min for EVG/c/FTC/TDF and EFV/FTC/TDF, respectively; *P* < .0001). Absolute changes in lipoprotein levels were similar between groups, with the exception of the high-density lipoprotein (HDL) cholesterol level, which increased more in the EFV/FTC/TDF group by week 48 (5 vs 8 mg/dL; *P* = .045). The absolute change in weight was greater in the EVG/c/FTC/TDF group from baseline to week 24 (0.9 and 0 kg for EVG/c/FTC/TDF and EFV/FTC/TDF, respectively; *P* = .01) but was similar between groups by week 48 (1 and 0.7 kg for EVG/c/FTC/TDF and EFV/FTC/TDF, respectively; *P* = .13). Glucose levels increased to a greater degree in the EFV/FTC/TDF group from baseline to week 48 (2 vs 5.5 mg/dL; *P* = .02). Changes in hemoglobin levels were similar between groups.

Factors Associated With sCD14 and Lp-PLA_2 Levels at Baseline

In an exploratory analysis, we determined factors independently associated with the log-transformed sCD14 level and the log-transformed Lp-PLA_2 level at baseline (Table 3). Factors independently associated with higher sCD14 levels prior to ART

Table 2. Baseline, Week 24, Week 48, and Absolute Change in Biomarker Levels, by Randomization Group

Biomarker, Time Point	EVG/c/FTC/TDF (n = 100)	EFV/FTC/TDF (n = 100)	*P* Values[a]
sCD14 level, ng/mL			
Week 0	1529.5 (1329–1843.5)	1593 (1328–1805.5)	.76
Week 24	1418 (1235–1642)	1649 (1454–1845)	<.0001
Week 48	1368.5 (1255–1560)	1654 (1436.5–1792)	<.0001
Absolute change			
Between weeks 0 and 24	−99 (−349.5 to 45)[b]	93 (−137.5 to 303.5)[b]	<.0001
Between weeks 0 and 48	−149 (−356 to 32.5)[b]	46 (−176.5 to 227)	<.0001
sCD163 level, ng/mL			
Week 0	861.15 (679.98–1213.75)	910.65 (728.9–1231.65)	.23
Week 24	579.2 (389.75–777.4)	549 (460–25–749.6)	.89
Week 48	517.7 (378.3–690.35)	525.2 (384.25–670.6)	.78
Absolute change			
Between weeks 0 and 24	−310 (−485.25 to–125.75)[b]	−355.5 (−583.4–221.35)[b]	.09
Between weeks 0 and 48	−337.4 (−514.8–185.15)[b]	−407.1 (−628.4–252.5)[b]	.05
sTNF-RI level, pg/mL			
Week 0	1186 (948.5–1476.5)	1172.5 (1017–1361)	.9
Week 24	1068.5 (872–1301.5)	1053.5 (917.5–1242.5)	.86
Week 48	1089 (907–1235)	1053 (881–1221.5)	.62
Absolute change			
Between weeks 0 and 24	−54 (−227.5 to 17)[b]	−103 (−215.5 to 6)[b]	.28
Between weeks 0 and 48	−120.5 (−230 to 16.5)[b]	−123 (−247.5 to 30)[b]	.47
IL-6 level, pg/mL			
Week 0	1.695 (1.205–2.475)	1.715 (1.27–2.765)	.6
Week 24	1.38 (0.93–2.2)	1.225 (0.905–2.42)	.77
Week 48	1.365 (0.885–2.08)	1.275 (0.895–2.185)	.91
Absolute change			
Between weeks 0 and 24	−0.205 (−0.905 to 0.185)[b]	−0.34 (−1.05 to 0.085)[b]	.55
Between weeks 0 and 48	−0.27 (−0.935 to 0.135)[b]	−0.365 (−1.2 to 0.14)[b]	.53
hsCRP level, ng/mL			
Week 0	1479 (506.5–4977)	1562.5 (751–3209.5)	.85
Week 24	1214.5 (467.5–3499.5)	1808.5 (781–4084)	.1
Week 48	1538 (542.5–3702.8)	1945.5 (745–4292.5)	.17
Absolute change			
Between weeks 0 and 24	−108 (−1755 to 637.7)	49.6 (−830 to 1793)	.04
Between weeks 0 and 48	−176.5 (−1872.5 to 860.5)[b]	55 (−662.5 to 1759.5)	<.01
Lp-PLA_2 level, ng/mL			
Week 0	171 (128.5–199)	158 (134.5–188)	.24
Week 24	157.5 (124.5–188)	167.5 (136–191)	.32
Week 48	156 (130–190)	165.5 (147.5–193)	.1
Absolute change			
Between weeks 0 and 24	−2 (−33 to 12)[b]	4.5 (−19 to 21)	.02
Between weeks 0 and 48	−6 (−30.5 to 22.5)	9 (−12 to 26.5)[b]	<.01

Data are median value (interquartile range).

Abbreviations: EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; EVG/c/FTC/TDF, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; Lp-PLA_2, lipoprotein-associated phospholipase A_2; sCD14, soluble CD14; sCD163, soluble CD163; sTNF-RI, soluble tumor necrosis factor α receptor I.

[a] For between-group differences.

[b] $P < .05$ for within-group comparisons.

initiation were lower weight, $CD4^+$ T-cell count, hemoglobin level, and low-density lipoprotein (LDL) cholesterol level and higher HIV-1 RNA load, HDL cholesterol level, triglycerides level, sTNF-RI level, and IL-6 level. Factors independently associated with a higher Lp-PLA_2 level prior to ART were male sex and higher total cholesterol and sTNF-RI levels.

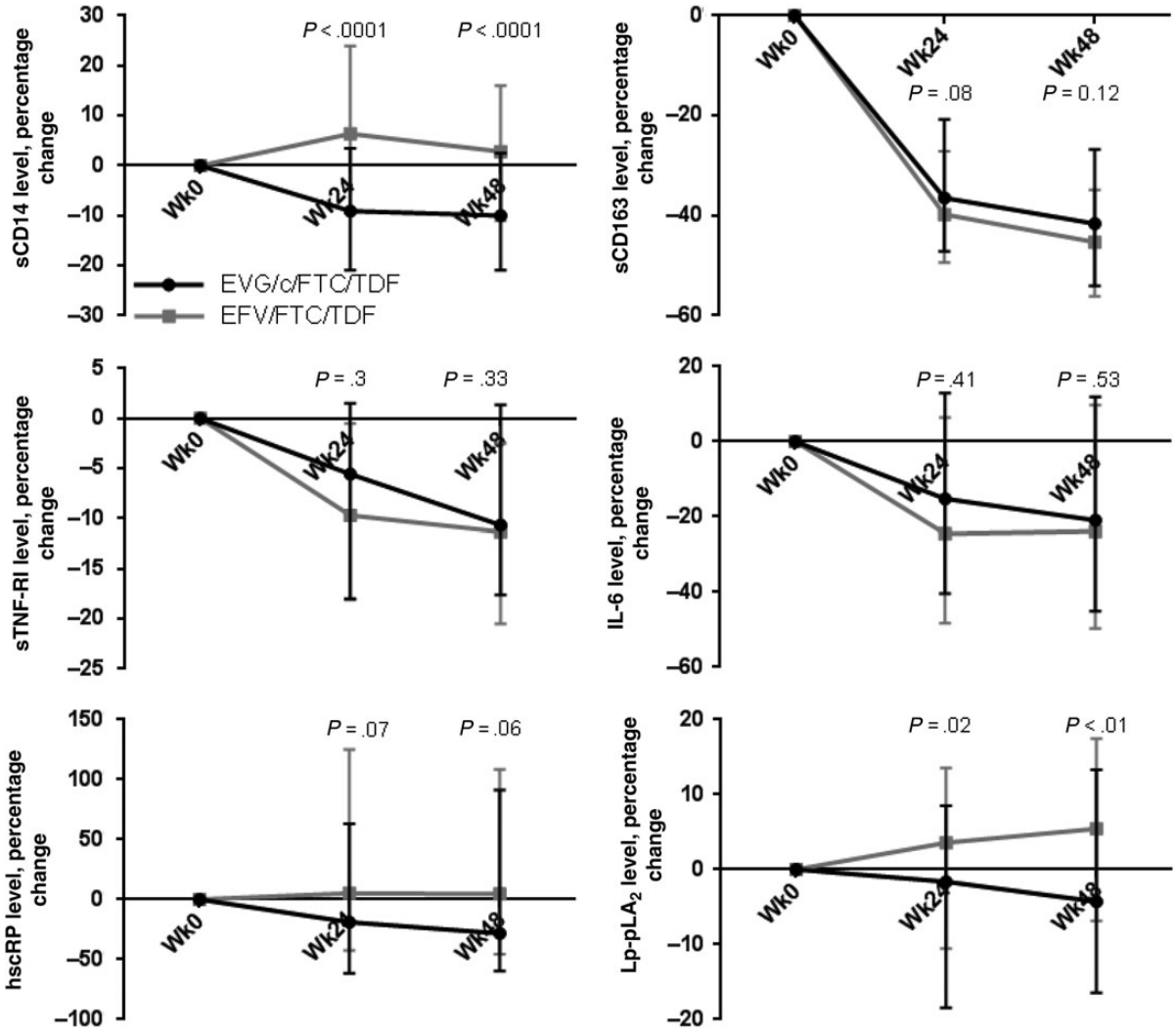

Figure 1. Median percentage changes (interquartile range) in biomarker levels over 24 and 48 weeks, by randomization group. *P* values are for comparisons between groups in the percentage change from weeks 0 to 24 and weeks 0 to 48. Abbreviations: EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; EVG/c/FTC/TDF, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; Lp-PLA_2, lipoprotein-associated phospholipase A_2; sCD14, soluble CD14; sCD163, soluble CD163; sTNF-RI, soluble tumor necrosis factor α receptor I.

Factors Associated With Change in sCD14 and Lp-PLA_2 Levels

We also determined factors independently associated with the percentage change from baseline to 48 weeks in log-transformed sCD14 and Lp-PLA_2 levels (Table 4). For percentage change from baseline to week 48 week in the log-transformed sCD14 level, randomization group remained independently associated in the final model, such that being randomly assigned to the EVG/c/FTC/TDF group was associated with a larger decline in the sCD14 level over 48 weeks. Additional factors that were independently associated with a larger decrease in the sCD14 level included higher baseline sCD14 level, lower baseline $CD4^+$ T-cell count, lower baseline HDL cholesterol level, larger increases in weight and eGFR, and larger decreases in sCD163 and hsCRP levels over 48 weeks. For percentage change from baseline to week 48 in the Lp-PLA_2 level, factors independently associated with a larger decrease in the Lp-PLA_2 level were higher baseline Lp-PLA_2 and IL-6 levels and a lower baseline LDL cholesterol level, as well as smaller increases in total cholesterol and triglycerides levels, a larger decrease in the sCD14 level, and a smaller decrease in the sCD163 level. Randomization group was not independently associated with percentage change in the Lp-PLA_2 level; however, after removing changes in sCD14 and sCD163 levels from the model, randomization group was associated with changes in the Lp-PLA_2 level. We considered that changes in monocyte activation could be in the causal pathway between randomization group and changes in the Lp-PLA_2 level, which is why changes in sCD14 and sCD163 levels were removed from this model.

Table 3. Factors Independently Associated With Soluble CD14 (sCD14) and Lipoprotein-Associated Phospholipase A_2 (Lp-PLA_2) Levels at Baseline

Variable	Parameter Estimate ± SE	*P* Values
Log sCD14 level[a]		
Weight, kg	$-2.43 \times 10^{-3} \pm 8.19 \times 10^{-4}$	<.01
$CD4^+$ T-cell count, cells/mm^3	$-1.77 \times 10^{-4} \pm 8.28 \times 10^{-5}$	.03
HIV-1 RNA load, copies/mL	$2.19 \times 10^{-7} \pm 7.25 \times 10^{-8}$	<.01
Hemoglobin level, g/dL	$-2.56 \times 10^{-2} \pm 9.88 \times 10^{-3}$	.01
HDL cholesterol level, mg/dL	$3.41 \times 10^{-3} \pm 1.6 \times 10^{-3}$	.03
LDL cholesterol level, mg/dL	$-1.13 \times 10^{-3} \pm 5.43 \times 10^{-4}$	.04
Triglycerides level, mg/dL	$5.73 \times 10^{-4} \pm 2.14 \times 10^{-4}$	<.01
Log sTNF-RI level, pg/mL	$0.348 \pm 5.94 \times 10^{-2}$	<.0001
Log IL-6 level, pg/mL	$7.67 \times 10^{-2} \pm 2.15 \times 10^{-2}$	<.001
Log Lp-PLA_2 level[b]		
Sex	$0.183 \pm 6.4 \times 10^{-2}$	<.01
Total cholesterol level, mg/dL	$1.99 \times 10^{-3} \pm 6.15 \times 10^{-4}$	<.01
Log sTNF-RI level	$0.315 \pm 7.3 \times 10^{-2}$	<.0001

Abbreviations: HDL, high-density lipoprotein; HIV-1, human immunodeficiency virus type 1; IL-6, interleukin 6; LDL, low-density lipoprotein; SE, standard error; sTNF-RI, soluble tumor necrosis factor α receptor I.

[a] Variables with a *P* value of < .25 in univariable analysis but not selected for inclusion in the final model included sex, race (white vs other), hepatitis C status, age, estimated glomerular filtration rate, log-transformed high-sensitivity C-reactive protein level, and log-transformed soluble CD163 level.

[b] Variables with a *P* value of < .25 in univariable analysis but not selected for in the final model included race (white vs other), hemoglobin level, triglycerides level, and log-transformed sCD14 level.

Table 4. Factors Independently Associated With Percentage Change in Soluble CD14 (sCD14) and Lipoprotein-Associated Phospholipase A_2 (Lp-PLA_2) Levels Over 48 Weeks

Variable	Parameter Estimate ± SE	*P* Values
Percentage change in log sCD14 level between wks 0 and 48[a]		
Randomization group	$-2.02 \times 10^{-2} \pm 3.05 \times 10^{-3}$	<.0001
Week 0 data on		
Log sCD14 level	$-5.44 \times 10^{-2} \pm 6.14 \times 10^{-3}$	<.0001
Log $CD4^+$ T-cell count	$6.3 \times 10^{-3} \pm 2.45 \times 10^{-3}$	.01
Log HDL cholesterol level	$1.04 \times 10^{-2} \pm 5.26 \times 10^{-3}$	.05
Percentage change between wks 0 and 48 in		
Log weight	-0.313 ± 0.104	<.01
Log eGFR	$-0.109 \pm 5.03 \times 10^{-2}$	.03
Log sCD163 level	$0.1 \pm 2.99 \times 10^{-2}$	<.01
Log hsCRP level	$3.11 \times 10^{-2} \pm 7.45 \times 10^{-3}$	<.0001
Percentage change in Lp-PLA_2 level between wks 0 and 48[b]		
Randomization group	$-2.64 \times 10^{-2} \pm 2.56 \times 10^{-2}$	.3
Week 0 data on		
Lp-PLA_2 level	$-1.87 \times 10^{-3} \pm 2.24 \times 10^{-4}$	<.0001
LDL cholesterol level	$1.23 \times 10^{-3} \pm 4.85 \times 10^{-4}$	.01
IL-6 level	$-2.56 \times 10^{-3} \pm 1.16 \times 10^{-3}$	.03
Percentage change between wks 0 and 48 in		
Total cholesterol level	$0.169 \pm 6.54 \times 10^{-2}$	.01
Triglycerides level	$5.33 \times 10^{-2} \pm 1.85 \times 10^{-2}$	<.01
sCD14 level	$0.229 \pm 6.19 \times 10^{-2}$	<.001
sCD163 level	$-0.122 \pm 5.4 \times 10^{-2}$	.02

Abbreviations: eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HIV-1, human immunodeficiency virus type 1; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDL, low-density lipoprotein; sCD163, soluble CD163; SE, standard error; sTNF-RI, soluble tumor necrosis factor α receptor I.

[a] Variables with a *P* value of < .25 in univariable analysis but not selected for in the final model included week 0 log-transformed weight, log-transformed HIV-1 RNA load, log-transformed eGFR, log-transformed hemoglobin level, log-transformed triglycerides level, log-transformed sCD163 level, log-transformed sTNF-RI level, log-transformed IL-6 level, and log-transformed hsCRP level and percentage change between weeks 0 and 48 in log-transformed $CD4^+$ T-cell count, log-transformed hemoglobin level, log-transformed HDL cholesterol level, log-transformed LDL cholesterol level, log-transformed triglycerides level, log-transformed sCD163 level, log-transformed sTNF-RI level, and log-transformed Lp-PLA_2 level.

[b] Variables with a *P* value of < .25 in univariable analysis but not selected for in the final model included week 0 randomization group, sex, weight, $CD4^+$ T-cell count, HIV-1 RNA level, eGFR, HDL cholesterol level, triglycerides level, sCD14 level, and sTNF-RI level and percentage change between weeks 0 and 48 in weight, $CD4^+$ T-cell count, HDL cholesterol level, and sTNF-RI level.

DISCUSSION

To date, there are limited data describing the differential effects of currently recommended first-line antiretroviral regimens on immune activation and inflammation during HIV infection. As long as viral suppression remains the goal of HIV treatment, choosing ART with the least long-term toxicity and highest benefit is of great priority in the management of this chronic illness. To our knowledge, this is the first study to compare the effects of ART initiation with an integrase inhibitor (elvitegravir)– and nonnucleoside reverse transcriptase inhibitor (NNRTI; efavirenz)– based regimen on markers of monocyte activation and systemic and vascular inflammation. We show here that, over 48 weeks, greater improvements in sCD14, hsCRP, and Lp-PLA_2 levels are achieved with EVG/c/FTC/TDF, compared with EFV/FTC/TDF.

In HIV infection, published studies have consistently demonstrated that ART initiation leads to decreases in levels of systemic markers of inflammation, with the exception of hsCRP [30–35], and decreased levels of immune activation [36, 37]. However, there are few studies that compare the effects of specific antiretrovirals and only one that included the integrase inhibitor class [34, 35, 38]. The results of these studies are consistent with findings for the EFV/FTC/TDF group in our study, in which levels of sTNF-RI and IL-6 decreased and the level of hsCRP remained similar. In a randomized, open-label trial of efavirenz or lopinavir/ritonavir (LPV/r) in combination with zidovudine/lamivudine initially, sTNF-RI and sTNF-RII levels decreased significantly over 24 weeks; however, the sTNF-RI level tended to increase to baseline by week 96, whereas decreases in the sTNF-RII level were maintained. There were no between-group differences in the changes observed [34]. In A5224s, a substudy of A5202, in which ART-naive, HIV-infected participants were

randomly assigned to receive abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC) with efavirenz or atazanavir/ritonavir (ATV/r) in a factorial design, changes in markers of inflammation over 24 and 96 weeks were evaluated. Levels of most markers, including sTNF-RI and sTNF-RII, TNF-α, IL-6, and adhesion molecules (sVCAM-1 and sICAM-1) decreased significantly by week 96, without significant differences between arms. However, the hsCRP level decreased less in ABC/3TC recipients, compared with TDF/FTC recipients, and at 96 weeks the hsCRP level was significantly higher than at baseline for the ABC/3TC plus efavirenz group [35]. Finally, to date, ACTG 5260s is the only ART initiation study that compared markers of immune activation and inflammation in the setting of an integrase inhibitor (raltegravir). This study randomly assigned ART-naive participants to receive TDF/FTC along with open-labeled raltegravir, ATV/r, or darunavir/ritonavir (DRV/r). In this study, the hsCRP level decreased with raltegravir and ATV/r by 96 weeks, the IL-6 level decreased with only raltegravir, the D-dimer level decreased with ATV/r and DRV/r, and levels of T-cell activation markers and sCD163 decreased in all groups [38]. Neither sTNF-RI nor Lp-PLA_2 levels were measured in this study.

Findings from our study are consistent with those from studies involving HIV-infected participants with virological suppression who were randomly assigned to continue their current regimen or switch to an integrase inhibitor-based regimen (raltegravir). In the SPIRAL study (n = 233), switch to raltegravir from a protease inhibitor (PI) led to improvements in hsCRP, IL-6, TNF-α, and D-dimer levels that could only partially be attributed to improvements in lipoprotein levels in the raltegravir arm [39]. Similarly, in the ANRS 138 trial (n = 164), immediate or delayed switch to raltegravir from an enfuvirtide-based regimen led to improvements in all inflammatory markers tested, including IL-6, hsCRP, and D-dimer levels [40]. Last, in a small study (n = 37), in which woman with virological suppression during their current PI- or NNRTI-based ART regimen were randomly assigned to undergo immediate or delayed switch to raltegravir, the sCD14 level (but not IL-6, hsCRP, or sCD163 levels) decreased significantly in both the immediate and delayed switch groups and was different between the raltegravir and PI/NNRTI groups at week 24 [41].

sCD14, a marker of monocyte activation and response to lipopolysaccharide, has been linked to subclinical atherosclerosis [11] and mortality [28] during HIV infection. In an observational study, the sCD14 level did not change over a 2-year study period in treatment-naive participants initiating ABC/3TC or TDF/FTC treatment along with EFV, LPV/r, or ATV/r [33]. The lack of decrease in the sCD14 level in the EFV/FTC/TDF group in our study is consistent with findings in this latter study. Interestingly, in our study, the sCD14 level decreased significantly by 24 weeks after initiation of the EVG-based regimen, a finding that may translate into a significant clinical benefit. Indeed, the association seen in our study between changes in sCD14 levels and Lp-PLA_2 levels could have significant mechanistic implications because monocytes and their products could be an important driver of vascular inflammation and atherosclerosis, a hypothesis supported by prior studies linking monocyte activation markers to noncalcified coronary plaques [25]; coronary calcifications [26]; aortic inflammation, as measured by positron emission tomography [9]; and acute coronary syndrome [42].

Lp-PLA_2, an enzyme produced by monocytes/macrophages, among other cells, that hydrolyzes oxidized phospholipids on LDL-cholesterol, thereby producing highly inflammatory mediators, has become an important marker of vascular inflammation and CVD risk, independent of other factors [43, 44]. An increased Lp-PLA_2 level predicts both primary and recurrent CVD events in the general population [29, 45] and has been used to further stratify patients with an intermediate 10-year risk for CVD [46]. In our study, the Lp-PLA_2 level decreased significantly in the EVG/c/FTC/TDF group, whereas an increase in the Lp-PLA_2 level was seen in the EFV/FTC/TDF group. Interestingly, while changes in Lp-PLA_2 levels were significantly different between the 2 groups, randomization group was only predictive of change in the Lp-PLA_2 level over 48 weeks when 2 monocyte activation markers, sCD14 and sCD163, were removed from the model. This suggests that the effect of EVG/c/FTC/TDF on Lp-PLA_2 may be mediated through a decrease in monocyte activation.

Mechanistically, it is possible that elvitegravir resulted in more-favorable changes in the sCD14 level owing to possibly higher concentration of drug in enterocytes [21], which could result in full suppression of viral replication in gut-associated lymphoid tissues and better control over bacterial translocation. Alternatively, since oxidized lipids are known to drive immune activation in the pathogenic development of coronary plaque [47–49] and because integrase inhibitors overall have more-favorable effect on lipids [19, 20], it is possible that integrase inhibitors decrease levels of oxidized lipids more than other classes of drugs, and this should be investigated. Last, it has been shown that integrase inhibitors cause a more rapid decline in the HIV-1 RNA level, compared with NNRTIs [24]. Although there was no difference in the proportion of participants achieving an HIV-1 RNA level of <50 copies/mL by 24 weeks in this study, it is possible that this contributed to the differences seen.

Strengths of this study include randomized treatment allocation and large sample size, compared with other published studies evaluating biomarkers longitudinally. Limitations include the relatively short duration over which changes in levels of the markers were evaluated. Although inflammation and immune activation likely improve most dramatically in the first year after ART initiation, a longer duration of follow-up would provide additional information, given that marker levels after suppressive ART are still higher than expected for HIV-uninfected

individuals [50]. Last, whether unboosted integrase inhibitors will lead to the same result is unknown. Therefore, these results should not be generalized to patients receiving unboosted integrase inhibitor–based regimens.

In conclusion, initiation of EVG/c/FTC/TDF therapy led to greater decreases in sCD14, hsCRP, and Lp-PLA_2 levels than EFV/FTC/TDF. Randomization group independently predicted changes in the sCD14 level, and changes in monocyte activation independently predicted changes in the Lp-PLA_2 level. There appears to be a favorable effect of the integrase inhibitor elvitegravir, compared with efavirenz, on HIV-related immune activation, which may, in turn, affect vascular inflammation.

Notes

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Potential conflicts of interest. V. S.-G., K. M., and J. S. are each employed by and hold stock in Gilead Sciences. G. A. M. has received research grants from BMS, Gilead Sciences, and GSK; has served as a consultant to BMS, GSK, and Merck; and has served as a speaker for BMS and Merck. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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