Journal of Infectious Diseases Advance Access published January 12, 2015

Differential Reduction in Monocyte Activation and Vascular Inflammation with Integrase Inhibitor-Based Initial Antiretroviral Therapy

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Abstract

Background: Little is known about how different antiretrovirals effect inflammation and monocyte activation in HIV infection.

Methods: We examined plasma obtained during a randomized, double-blind trial in ART-naïve HIV-infected adults comparing efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir (EVG/c/FTC/TDF) and efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF). From a random sample achieving HIV-1 RNA<50 copies/mL by week 48, changes over 24 and 48 weeks in biomarkers of monocyte activation (sCD14, sCD163), systemic (sTNF-RI, IL-6, hsCRP) and vascular inflammation (Lp-PLA_2) were compared. Multivariable linear regression was employed.

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

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

Introduction

Advances in antiretroviral therapy (ART) have had an impressive impact on morbidity and mortality due to HIV over the last two 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 may accelerate faster with age than the general population[6].

While traditional CVD risk factors[7] and antiretroviral therapy[8] have been implicated in risk of CVD in HIV infection, 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 on ART may be the result of enterocyte damage leading to microbial translocation[12, 13], co-infections[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 as 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 as there many medications available to choose from for the treatment of HIV infection and 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 markers of monocyte activation as well as systemic and vascular inflammation between ART-naïve HIV-infected adults randomized 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, 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-blind, active-controlled clinical trial to evaluate the safety and efficacy of EVG/c/FTC/TDF versus EFV/FTC/TDF in HIV-infected ART-naïve adults. The entry criteria for this study have been published[24]. In brief, eligibility criteria were age ≥ 18 years, HIV-1 RNA level ≥ 5,000 copies/mL, no prior ART use, genotypic susceptibility to emtricitabine, tenofovir and efavirenz, estimated glomerular filtration rate (eGFR) ≥ 70 ml/min by Cockcroft-Gault equation, liver transaminases ≤ 5 x upper limit of normal, absolute neutrophil count ≥ 1,000/mm^3, platelets ≥ 50,000/mm^3, hemoglobin ≥ 8.5 g/dL, life expectancy ≥ 1 year, 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 randomized 1:1 to receive EVG/c/FTC/TDF or EFV/FTC/TDF both with matching placebo. The participants for this study were a random sample of Gilead 102 participants who achieved HIV-1 RNA level < 50 copies/mL by week 48 and had stored plasma available from entry, week 24 and week 48 visits. All participants of the Gilead 102 study signed written informed consent which included consent for use of stored blood 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 markers of monocyte activation, ie, soluble CD14 (sCD14) and soluble CD163 (sCD163), indices of systemic inflammation, ie, soluble tumor necrosis factor α receptor-I (sTNF-RI), interleukin-6

(IL-6) and high sensitivity C-reactive protein (hsCRP), and vascular inflammation, ie, lipoprotein-associated phospholipase A_2 (Lp-PLA_2). Secondary outcomes of interest were changes in these same 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 drawn after an 8 hour fast at entry, week 24 and week 48. Plasma was stored at -80°C and never thawed until analysis. Stored plasma samples were analyzed using specific enzyme-linked immunosorbent assay (ELISA) kits as per the manufacturers' instructions (R&D Systems, Minneapolis, MN, USA for all except diaDexus, Inc., CA, USA for Lp-PLA_2). Markers with compelling data linking them to CVD risk and mortality in HIV were selected[25-29].

Statistical analysis

Demographics, clinical indices and HIV-related factors are presented overall and by group at baseline. Median and interquartile range (IQR) are reported for continuous variables and frequency and percent for categorical variables. Absolute and percent change from baseline to week 24 and from baseline to week 48 in markers of monocyte activation and inflammation as well as clinically relevant variables were determined. All baseline variables and endpoints were compared between groups using unpaired t-tests or Wilcoxon Rank Sum tests as warranted by distribution for continuous variables and by Chi-Square tests, Fisher's Exact tests, or Pearson Exact Chi-Square tests as appropriate for categorical variables. Within-group changes were tested using paired t-tests or Wilcoxon Signed Rank tests as appropriate for the distribution.

For the regression analyses, all non-normally distributed variables were log-transformed prior to model fitting. Univariable followed by multivariable linear regression was used to explore

relationships of baseline factors with baseline log-sCD14 and log-Lp-PLA_2. Variables tested in the univariable analyses included: age, sex, race, hepatitis B and C status, weight, CD4+ cell count, HIV-1 RNA level, eGFR, hemoglobin level, glucose level, lipoprotein levels, other markers of monocyte activation and inflammation at baseline. All those variables with $p<0.25$ in univariable analyses were considered for inclusion in the multivariable model and backward elimination was used for model selection. Next, two separate analyses were performed where change in sCD14 and Lp-PLA2 were the outcomes. First, ANCOVA was used to adjust mean percent change from baseline to week 48 in log-sCD14 and Lp-PLA_2 for baseline levels of these two markers respectively and for percent changes from baseline to week 48 in clinically relevant variables, including weight, CD4+ 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 percent change from baseline to week 48 in log-sCD14 and Lp-PLA_2. Variables tested in the univariable analyses for models with percent change from baseline to week 48 in log-sCD14 or Lp-PLA_2 as the outcome included: all above baseline variables as well as percent change from baseline to week 48 in weight, CD4+ 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 two-sided and considered significant with $p<0.05$. Adjustments were not made in this significance level for multiple comparisons. Analyses were performed using SAS v. 9.2 (The SAS Institute, Carey, North Carolina, USA).

With 200 participants in this study and assuming a conservative common standard deviation of 10%, our study had 80% power to detect a between-group difference in percent change over 48

weeks in the tested biomarkers as low as 4% using an unpaired t test with a two-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 two treatment groups were balanced with regard to all demographic and HIV-related factors except there were more participants on anti-hypertensive medications in the EVG/c/FTC/TDF group (18 vs 8%; p=0.04). When comparing individual classes of anti-hypertensive medications, only diuretic use was higher in the EVG/c/FTC/TDF group (13 vs 3%; p<0.01); proportion of participants on other classes were similar between groups (Table 1). Overall, the median (IQR) age was 38 (30-44.5) years and the majority of participants were men (89%) and Caucasian (65%); 30% were African American and 5% from other racial groups. Baseline weight was 81 (70.5-92.6) kg and eGFR was 120.2 (99.2-137.2) ml/min. Three and five participants had chronic Hepatitis B and C infections, respectively. All participants were ART-naïve at study entry by design with baseline CD4+ cell count 371.5 (267.5-484.5) cell/mm^3 and HIV-1 RNA 64,900 (25,050-147,000) copies/mL. At baseline, 10% were on at least one cholesterol-lowering medication, including four participants on an HMG-CoA reductase inhibitor or statin.

Changes in markers after ART

At baseline, markers of monocyte activation, systemic and vascular inflammation were similar between-groups. Baseline, week 24, week 48 and absolute changes from baseline to week 24 and to week 48 in all markers are shown in Table 2. Within the EVG/c/FTC/TDF group, all markers decreased significantly relative to baseline by week 48 with the exception of Lp-PLA$_2$

which neared significance (p=0.06 within-group). In the EFV/FTC/TDF group, the changes were mixed. Over 48 weeks, sCD163, sTNF-RI and IL-6 decreased significantly; however, Lp-PLA_2 increased, and sCD14 and hsCRP did not change significantly. Percent changes in the markers are shown in Figure 1. Within-group analyses evaluating percent change in the markers were similar to the absolute changes except, within the EVG/c/FTC/TDF group, change in hsCRP was not statistically significant; and, in the EFV/FTC/TDF group, increases in sCD14 and hsCRP were significant at both week 24 and 48. Absolute and percent 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 with changes favoring the EVG/c/FTC/TDF group. Changes were similar between groups for sCD163, sTNF-RI and IL-6. After adjustment for percent changes from baseline to week 48 in weight, CD4+ cell count, hemoglobin level, eGFR, glucose level and lipoprotein levels, percent change from baseline to week 48 in sCD14 and Lp-PLA_2 remained significantly different between groups with changes favoring EVG/c/FTC/TDF (data not shown).

Changes in other clinically relevant factors after ART

In this sample, absolute changes in CD4+ cell count from baseline to week 24 and from baseline to week 48 were similar between groups (+185 vs +155 cells/mm^3 for EVG/c/FTC/TDF vs EFV/FTC/TDF; p=0.24 and +246 vs 217 /mm^3; p=0.23, respectively) as was the proportion of participants achieving HIV-1 RNA level <50 copies/mL by week 24 (95% vs 96% for EVG/c/FTC/TDF vs EFV/FTC/TDF; p=0.72). By design, all participants had undetectable HIV-1 RNA level by week 48. Decline in eGFR was greater in the EVG/c/FTC/TDF group and this was apparent by week 24 (-11.3 vs -0.2 ml/min for EVG/c/FTC/TDF vs EFV/FTC/TDF; p<0.0001). Absolute changes in lipoprotein levels were similar between groups with the exception of HDL-cholesterol which increased more in the EFV/FTC/TDF group by week 48 (+5 vs +8 mg/dL for EVG/c/FTC/TDF vs EFV/FTC/TDF; p=0.045). Absolute change in weight was greater in the

EVG/c/FTC/TDF group from baseline to week 24, but was similar between groups by week 48 (+0.9 vs 0 kg for EVG/c/FTC/TDF vs EFV/FTC/TDF; p=0.01 and +1 vs 0.7 kg; p=0.13). 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=0.02). Changes in hemoglobin levels were similar between groups.

Factors associated with sCD14 and Lp-PLA$_2$ at baseline

In an exploratory analysis, we determined factors independently associated with log-sCD14 and log-Lp-PLA$_2$ at baseline (Table 3). Factors independently associated with higher sCD14 levels prior to ART initiation were lower weight, CD4+ cell count, hemoglobin and LDL-cholesterol levels, and higher HIV-1 RNA, HDL-cholesterol, triglyceride, sTNF-RI and IL-6 levels. Factors independently associated with higher Lp-PLA$_2$ prior to ART were male sex, and higher total cholesterol and sTNF-RI levels.

Factors associated with change in sCD14 and Lp-PLA$_2$

We also determined factors independently associated with percent change from baseline to 48 weeks in log-sCD14 and Lp-PLA$_2$ (Table 4). For percent change from baseline to 48 weeks in log-sCD14, randomization group remained independently associated in the final model such that being randomized to EVG/c/FTC/TDF was associated with a larger decline in sCD14 over 48 weeks. Additional factors that were independently associated with a larger decrease in sCD14 included higher baseline sCD14, lower baseline CD4+ cell count, lower baseline HDL-cholesterol, larger increases in weight and eGFR, and larger decreases in sCD163 and hsCRP over 48 weeks. For percent change from baseline to 48 weeks in Lp-PLA$_2$, factors independently associated with a larger decrease in Lp-PLA$_2$ were higher baseline Lp-PLA$_2$ and IL-6, and lower baseline LDL-cholesterol, as well as smaller increases in total cholesterol and triglycerides, a larger decrease in sCD14 and a smaller decrease in sCD163. Randomization group was not independently associated with percent change in Lp-PLA$_2$; however, after

removing changes in sCD14 and sCD163 from the model, randomization group was associated with changes in Lp-PLA_2. We considered that changes in monocyte activation could be in the causal pathway between randomization group and change in Lp-PLA_2 and that is why changes in sCD14 and sCD163 were removed from this model.

Discussion

To date, there are limited data describing the differential effects of currently recommended first line antiretroviral regimens on immune activation and inflammation in 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 a non-nucleoside reverse transcriptase inhibitor (NNRTI) (efavirenz)-based regimen on markers of monocyte activation, systemic and vascular inflammation. We show here that over 48 weeks, changes in sCD14, hsCRP and Lp-PLA_2 favor EVG/c/FTC/TDF over EFV/FTC/TDF.

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

HIV-infected participants were randomized to abacavir/lamuvudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC) with EFV or atazanavir/ritonavir (ATV/r) in a factorial design, changes in markers of inflammation over 24 and 96 weeks where evaluated. Most markers, including sTNF-RI and sTNF-RII, tumor necrosis factor-α, IL-6 and adhesion molecules (sVCAM-1 and sICAM-1) decreased significantly by week 96, without significant differences between arms. However, hsCRP decreased less in those on ABC/3TC than among TDF/FTC recipients and at 96 weeks hsCRP was significantly higher than baseline for the ABC/3TC plus EFV 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 randomized ART-naïve participants to receive TDF/FTC along with open-labeled raltegravir, ATV/r or darunavir/ritonavir (DRV/r). In this study, hsCRP decreased with raltegravir and ATV/r by 96 weeks; IL-6 decreased with only raltegravir; D-dimer decreased with ATV/r and DRV/r; markers of T cell activation and sCD163 decreased in all groups[38]. Neither sTNF-RI nor Lp-PLA_2 were measured in this study.

Our study is consistent with studies in virologically-suppressed HIV-1 infected participants randomized 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, tumor necrosis factor-α and D-dimer which 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[40]. Last, in a small study (N=37) where woman who were virologically suppressed on their current PI- or NNRTI-based ART were randomized to immediate or delayed switch to raltegravir, sCD14 (but not IL-6, hs-CRP, or sCD163) decreased significantly in both the

immediate and delayed switch groups and was different between the raltegravir and PI/NNRTI groups at week 24[41].

Soluble CD14, a marker of monocyte activation and response to lipopolysaccharide, has been linked to subclinical atherosclerosis[11] and mortality in HIV[28]. In an observational study, sCD14 did not change over a two year study period in treatment-naïve participants initiating ABC/3TC or TDF/FTC with EFV, LPV/r or ATV/r[33]. The lack of decrease in sCD14 in the EFV/FTC/TDF group in our study is consistent with this latter study. Interestingly, in our study, sCD14 significantly decreased by 24 weeks after initiation of the EVG-based regimen, a finding that may translate to significant clinical benefit. Indeed, the association seen in our study between changes in sCD14 and in Lp-PLA_2 could have significant mechanistic implications as 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 measured by positron emission tomography[9] and to acute coronary syndrome[42].

Lipoprotein-associated phospholipase A_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]. Increased Lp-PLA_2 predicts both primary and recurrent CVD events in the general population[29, 45] and has been utilized to further stratify patients at intermediate 10 year CVD risk[46]. In our study, Lp-PLA_2 decreased in the EVG/c/FTC/TDF group significantly whereas an increase in Lp-PLA_2 was seen in the EFV/FTC/TDF group. Interestingly, while the changes in Lp-PLA_2 were significantly different between the two groups, randomization group was only predictive of change in Lp-PLA_2 over 48 weeks when two 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 sCD14 due 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 integrase inhibitors overall have more favorable effect on lipids[19, 20], it is possible that integrase inhibitors decrease 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 HIV-1 RNA level compared to NNRTIs[24]. Although there was no difference in the proportion of participants achieving an HIV-1 RNA level < 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 to other published studies evaluating biomarkers longitudinally. Limitations include the relatively short duration over which changes in the markers were evaluated. Although inflammation and immune activation likely improve most dramatically in the first year after antiretroviral initiation, longer duration of follow-up would provide additional information given 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 on unboosted integrase inhibitor based regimens.

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

Acknowledgements: This study was supported by an investigator initiated research grant from Gilead to GAM and by K23HL116209 to COH. Technical assistance was provided by the Center for AIDS Research at Case Western Reserve University (AI 36219). Conflicts of Interest: VG, KM and JS are each employed by and hold stock in Gilead Sciences. GAM 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 conflicts.

Table 1—Baseline Demographic, Clinical and HIV-Related Indices by Randomization Group

	EVG/c/FTC/TDF n=100	EFV/FTC/TDF n=100	p
Age, years	37 (30.5-44.5)	38 (30-44.5)	0.98
Men	88 (88)	90 (90)	0.65
Race			0.69
Caucasian	62 (62)	67 (67)	
African American	33 (33)	26 (26)	
Other	5 (5)	7 (7)	
Chronic Hepatitis B	0 (0)	3 (3)	0.25
Chronic Hepatitis C	2 (2)	3 (3)	>0.99
Weight, Kg	80.7 (69.6-89.8)	81.2 (71.5-95.3)	0.37
eGFR, ml/min	116.3 (97.8-139.4)	121.5 (101.1-135.6)	0.58
Hemoglobin, g/dL	14.2 (12.9-15.1)	14.3 (13.5-14.9)	0.49
Glucose, mg/dL	92 (86-98)	91 (84-97)	0.37
Total cholesterol, mg/dL	161.5 (139-181)	161.5 (141-185)	0.72
LDL-cholesterol, mg/dL	98 (79.5-118)	94.5 (82-115)	0.9
HDL-cholesterol, mg/dL	41 (35-48)	40 (33-47)	0.28
Triglycerides, mg/dL	98 (79.5-118)	100.5 (78-152)	0.39
Anti-hypertensive(s)[a]	18 (18)	8 (8)	0.04
Anti-hypertensive class			
Renin-angiotensin system agent	12 (12)	8 (8)	0.35
Beta-blocker	3 (3)	0 (0)	0.08
Calcium channel blocker	2 (2)	2 (2)	>0.99
Diuretic	13 (13)	3 (3)	<0.01
Cholesterol-lowering agent(s)[a]	11 (11)	9 (9)	0.64
Cholesterol-lowering class			
Statin	2 (2)	2 (2)	>0.99
Fish oil	8 (8)	7 (7)	0.79

Fibrate	2 (2)	0 (0)	0.16
CD4 cell count, cells/mm^3	369 (279.5-473)	380.5 (249-492)	0.96
HIV-1 RNA, copies/mL	52,850 (19,550-144,000)	79,300 (36,750-150,500)	0.08

Continuous variables reported as median (interquartile range) and categorical variables as frequency (percent)

[a]On one or more anti-hypertensive or cholesterol-lowering medication

Table 2—Baseline, Week 24, Week 48 and Absolute Change in Biomarkers by Randomization Group

	EVG/c/FTC/TDF n=100	EFV/FTC/TDF n=100	p-value[a]
sCD14, ng/mL			
Week 0	1529.5 (1329-1843.5)	1593 (1328-1805.5)	0.76
Week 24	1418 (1235-1642)	1649 (1454-1845)	<0.0001
Week 48	1368.5 (1255-1560)	1654 (1436.5-1792)	<0.0001
0-24 week change[b]	-99 (-349.5-45)[c]	93 (-137.5-303.5)[c]	<0.0001
0-48 week change[b]	-149 (-356-32.5)[c]	46 (-176.5-227)	<0.0001
sCD163, ng/mL			
Week 0	861.15 (679.98-1213.75)	910.65 (728.9-1231.65)	0.23
Week 24	579.2 (389.75-777.4)	549 (460-25-749.6)	0.89
Week 48	517.7 (378.3-690.35)	525.2 (384.25-670.6)	0.78
0-24 week change[b]	-310 (-485.25--125.75)[c]	-355.5 (-583.4--221.35)[c]	0.09
0-48 week change[b]	-337.4 (-514.8--185.15)[c]	-407.1 (-628.4--252.5)[c]	0.05
sTNF-RI, pg/mL			
Week 0	1186 (948.5-1476.5)	1172.5 (1017-1361)	0.9
Week 24	1068.5 (872-1301.5)	1053.5 (917.5-1242.5)	0.86
Week 48	1089 (907-1235)	1053 (881-1221.5)	0.62
0-24 week change[b]	-54 (-227.5-17)[c]	-103 (-215.5—6)[c]	0.28
0-48 week change[b]	-120.5 (-230-16.5)[c]	-123 (-247.5--30)[c]	0.47
IL-6, pg/mL			
Week 0	1.695 (1.205-2.475)	1.715 (1.27-2.765)	0.6
Week 24	1.38 (0.93-2.2)	1.225 (0.905-2.42)	0.77
Week 48	1.365 (0.885-2.08)	1.275 (0.895-2.185)	0.91
0-24 week change[b]	-0.205 (-0.905-0.185)[c]	-0.34 (-1.05-0.085)[c]	0.55

0-48 week change[b]	-0.27 (-0.935-0.135)[c]	-0.365 (-1.2-0.14)[c]	0.53
hsCRP, ng/mL			
Week 0	1479 (506.5-4977)	1562.5 (751-3209.5)	0.85
Week 24	1214.5 (467.5-3499.5)	1808.5 (781-4084)	0.1
Week 48	1538 (542.5-3702.8)	1945.5 (745-4292.5)	0.17
0-24 week change[b]	-108 (-1755-637.7)	49.6 (-830-1793)	0.04
0-48 week change[b]	-176.5 (-1872.5-860.5)[c]	55 (-662.5-1759.5)	<0.01
Lp-PLA$_2$, ng/mL			
Week 0	171 (128.5-199)	158 (134.5-188)	0.24
Week 24	157.5 (124.5-188)	167.5 (136-191)	0.32
Week 48	156 (130-190)	165.5 (147.5-193)	0.1
0-24 week change[b]	-2 (-33-12)[c]	4.5 (-19-21)	0.02
0-48 week change[b]	-6 (-30.5-22.5)	9 (-12-26.5)[c]	<0.01

Values shown are median (interquartile range)

sCD14, soluble CD14; sCD163, soluble CD163; sTNF-RI, soluble tumor necrosis factor α receptor-I; IL-6, interleukin-6; hsCRP, high sensitivity C-reactive protein, Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$

[a]p-value for between-group test

[b]Absolute change

[c]p<0.05 within-group

Table 3—Factors Independently Associated with sCD14 and Lp-PLA$_2$ at Baseline

Variable	Parameter Estimate (Standard Error)	p-value
Log-sCD14[a]		
Weight, Kg	-2.43×10^{-3} (8.19×10^{-4})	<0.01
CD4 Count, cells/mm^3	-1.77×10^{-4} (8.28×10^{-5})	0.03
HIV-1 RNA, copies/mL	2.19×10^{-7} (7.25×10^{-8})	<0.01
Hemoglobin, g/dL	-2.56×10^{-2} (9.88×10^{-3})	0.01
HDL-cholesterol, mg/dL	3.41×10^{-3} (1.6×10^{-3})	0.03
LDL-cholesterol, mg/dL	-1.13×10^{-3} (5.43×10^{-4})	0.04
Triglycerides, mg/dL	5.73×10^{-4} (2.14×10^{-4})	<0.01
Log-sTNF-RI, pg/mL	0.348 (5.94×10^{-2})	<0.0001
Log-IL-6, pg/mL	7.67×10^{-2} (2.15×10^{-2})	<0.001
Log- Lp-PLA$_2$[b]		
Sex	0.183 (6.4×10^{-2})	<0.01
Total cholesterol, mg/dL	1.99×10^{-3} (6.15×10^{-4})	<0.01
Log-sTNF-RI	0.315 (7.3×10^{-2})	<0.0001

sCD14, soluble CD14; sTNF-RI, soluble tumor necrosis factor α receptor I; IL-6, interleukin-6, Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$

[a] Variables with p<0.25 in univariable analysis, but not selected for in the final model included: sex, race (Caucasian vs other), Hepatitis C status, age, eGFR, log-transformed high sensitivity C-reactive protein and log-transformed soluble CD163

[b] Variables with p<0.25 in univariable analysis, but not selected for in the final model included: race (Caucasian vs other), hemoglobin, triglyceride level, log-transformed soluble CD14

Table 4—Factors Independently Associated with Percent Change Over 48 Weeks in sCD14 and Lp-PLA_2

Variable	Parameter Estimate (Standard Error)	p-value
0-48 week % change in log-sCD14[a]		
Randomization group	-2.02×10^{-2} (3.05×10^{-3})	<0.0001
Baseline log-sCD14, ng/mL	-5.44×10^{-2} (6.14×10^{-3})	<0.0001
Baseline log-CD4 count, cells/mm3	6.3×10^{-3} (2.45×10^{-3})	0.01
Baseline log-HDL-cholesterol, mg/dL	1.04×10^{-2} (5.26×10^{-3})	0.05
0-48 week % change log-weight, %	-0.313 (0.104)	<0.01
0-48 week % change log-eGFR, %	-0.109 (5.03×10^{-2})	0.03
0-48 week % change log-sCD163, %	0.1 (2.99×10^{-2})	<0.01
0-48 week % change log-hsCRP, %	3.11×10^{-2} (7.45×10^{-3})	<0.0001
0-48 week % change in Lp-PLA_2[b]		
Randomization group	-2.64×10^{-2} (2.56×10^{-2})	0.3
Baseline Lp-PLA_2, ng/mL	-1.87×10^{-3} (2.24×10^{-4})	<0.0001
Baseline LDL-cholesterol, mg/dL	1.23×10^{-3} (4.85×10^{-4})	0.01
Baseline IL-6, pg/mL	-2.56×10^{-3} (1.16×10^{-3})	0.03
0-48 week % change total cholesterol, %	0.169 (6.54×10^{-2})	0.01
0-48 week % change triglycerides, %	5.33×10^{-2} (1.85×10^{-2})	<0.01
0-48 week % change sCD14, %	0.229 (6.19×10^{-2})	<0.001
0-48 week % change in sCD163, %	-0.122 (5.4×10^{-2})	0.02

sCD14, soluble CD14; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate by Cockcroft-Gault; sCD163, soluble CD163; hsCRP, high sensitivity C-reactive protein; Lp-

PLA_2, lipoprotein-associated phospholipase A_2; LDL, low density lipoprotein; IL-6, interleukin-6; sCD163, soluble CD163

[a] Variables with p<0.25 in univariable analysis, but not selected for in the final model included: baseline log-weight, log-HIV-1 RNA level, log-estimated glomerular filtration rate, log-hemoglobin, log-triglyceride level, log-soluble CD163, log-soluble tumor necrosis factor alpha receptor-I, log-interleukin-6, log-high sensitivity C-reactive protein; and percent change from baseline to week 48 in log-CD4+ cell count, log-hemoglobin, log-HDL-cholesterol, log-LDL-cholesterol, log-triglyceride level, log-soluble CD163, log-soluble tumor necrosis factor alpha receptor-I and log-lipoprotein-associated phospholipase A_2

[b] Variables with p<0.25 in univariable analysis, but not selected for in the final model included: baseline randomization group, sex, weight, CD4+ cell count, HIV-1 RNA level, estimated glomerular filtration rate, HDL-cholesterol, triglyceride level, soluble CD14, soluble tumor necrosis factor alpha receptor-I; and percent change from baseline to week 48 in weight, CD4+ cell count, HDL-cholesterol, soluble tumor necrosis factor alpha receptor-I

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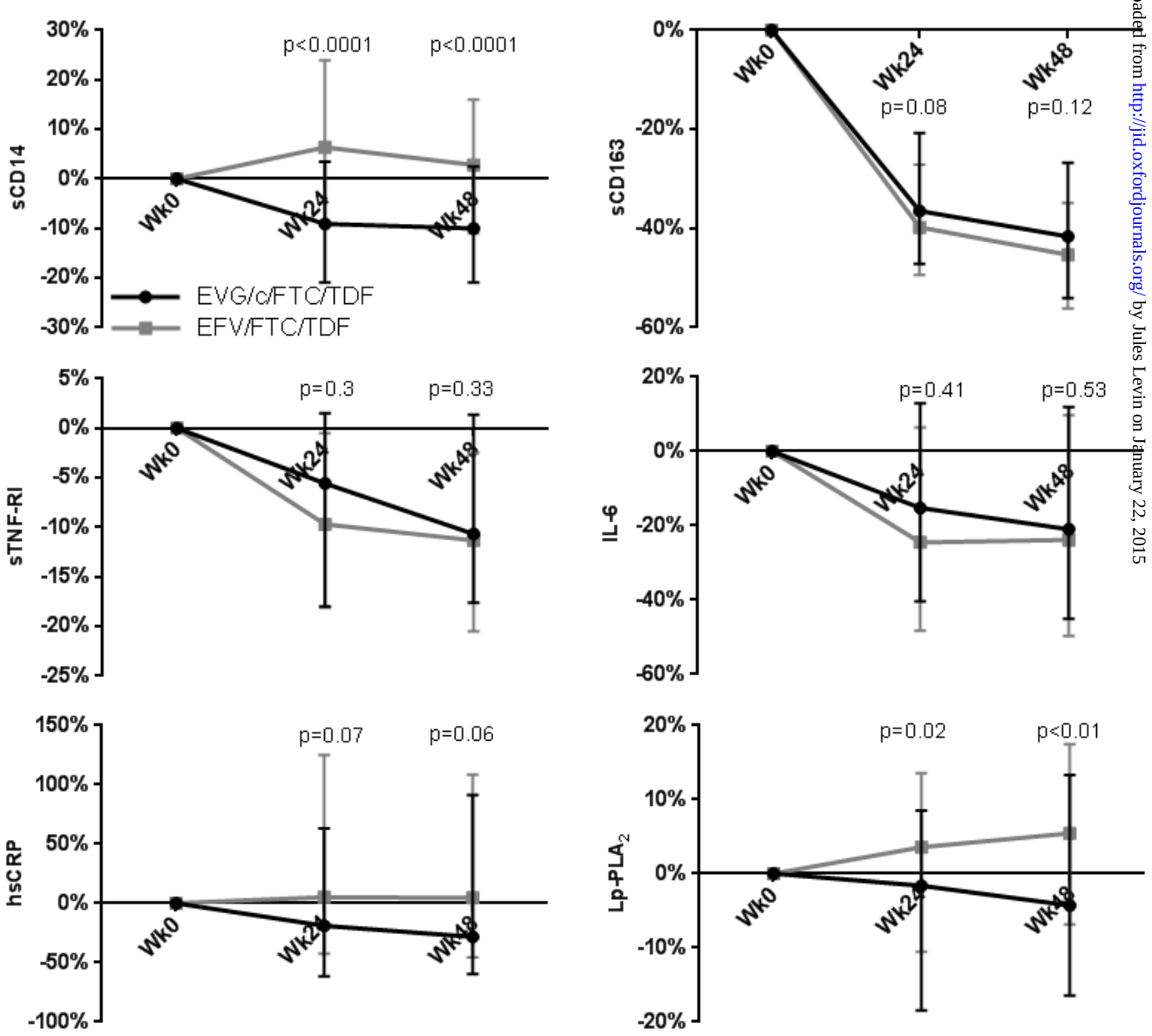
Figure 1--Median % Change over 24 and 48 Weeks for Each Biomarker by Group



P-values shown are for comparisons between-groups for percent change from 0 to 24 and 0 to 48 weeks, respectively. Error bars shown are interquartile range.