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Elvitegravir Reduces Monocyte Activation and Vascular Inflammation More than Efavirenz

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BACKGROUND:

- Heightened inflammation and monocyte activation may drive cardiovascular disease and other comorbidities in HIV.[1,2]
- Little is known about the comparative effects of specific antiretrovirals on inflammation and immune activation in HIV.

METHODS:

- We examined plasma obtained during a randomized, double-blind trial in ART-naïve HIV-infected adults comparing the efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir (EVG/c/FTC/TDF) and efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF) (Gilead 102).[3]

ELIGIBILITY CRITERIA[3]

- HIV-1 infection
- 18 years or older
- HIV-1 RNA ≥5,000 copies/ml
- ART-naïve with genotypic susceptibility to FTC, TDF and EFV
- eGFR ≥70 ml/min; liver transaminases ≤5x ULN
- ANC ≥1,000/mm^3; PLT ≥50,000/mm^3; Hgb ≥8.5 g/dL
- Life expectancy ≥1 year; no AIDS-defining conditions within 30 days
- Not on HCV treatment, other meds known to interact or corticosteroids
- No active infection or malignancy
- Alcohol or substance use that would interfere with study compliance

- 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.
- Markers were measured by specific ELISA (R&D Systems, Minneapolis, MN, USA for all except diaDexus, Inc., CA, USA for Lp-PLA$_2$).

STATISTICAL ANALYSES:

- Within- and between-group comparisons were made using t tests or Wilcoxon tests as appropriate.
- ANCOVA was used to adjust mean 0-48 week %changes in sCD14 and Lp-PLA$_2$ for baseline levels of these two markers and for 0-48 week %changes in clinically relevant factors.
- Univariable followed by multivariable linear regression were used to explore relationships of baseline sCD14 and Lp-PLA$_2$ and changes in these two markers with available demographics, labs, HIV-related factors and other markers.

Baseline Demographic, Clinical and HIV-Related Indices by 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)	18 (18)	8 (8)	0.04
Anti-hypertensive class			
Renin-angiotensin 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)	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+ 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 (IQR) and categorical variables as frequency (percent)

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

Variable	Parameter Estimate (Standard Error)	p
Log-sCD14		
Weight, kg	-2.43x10^{-3} (8.19x10^{-4})	<0.01
CD4 Count, cells/mm^3	-1.77x10^{-4} (8.28x10^{-5})	0.03
HIV-1 RNA, copies/mL	2.19x10^{-7} (7.25x10^{-8})	<0.01
Hemoglobin, g/dL	-2.56x10^{-2} (9.88x10^{-3})	0.01
HDL-cholesterol, mg/dL	3.41x10^{-3} (1.6x10^{-3})	0.03
LDL-cholesterol, mg/dL	-1.13x10^{-3} (5.43x10^{-4})	0.04
Triglycerides, mg/dL	5.73x10^{-4} (2.14x10^{-4})	<0.01
Log-sTNF-RI, pg/mL	0.348 (5.94x10^{-2})	<0.0001
Log-IL-6, pg/mL	7.67x10^{-2} (2.15x10^{-2})	<0.001
Log- Lp-PLA$_2$		
Sex	0.183 (6.4x10^{-2})	<0.01
Total cholesterol, mg/dL	1.99x10^{-3} (6.15x10^{-4})	<0.01
Log-sTNF-RI	0.315 (7.3x10^{-2})	<0.0001

Variables considered: age, sex, race, hepatitis B and C status, weight, CD4+ count, HIV-1 RNA level, eGFR, hemoglobin, glucose, lipoprotein levels, other markers of monocyte activation and inflammation at baseline

Baseline and Absolute Change in Biomarkers and Other Clinical Factors by Group

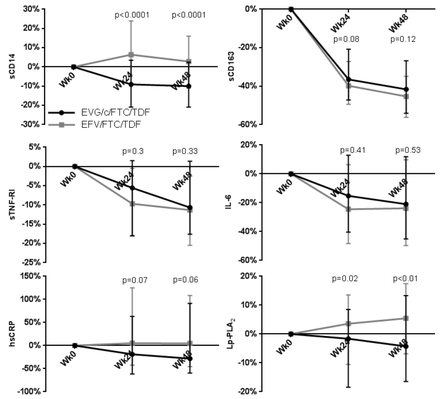
	EVG/c/FTC/TDF n=100	EFV/FTC/TDF n=100	p
sCD14, ng/mL			
Week 0	1529.5 (1329-1843.5)	1593 (1328-1805.5)	0.76
0-24 week change	**-99 (-349.5-45)[a]**	**93 (-137.5-303.5)[a]**	**<0.0001**
0-48 week change	**-149 (-356-32.5)[a]**	**46 (-176.5-227)**	**<0.0001**
sCD163, ng/mL			
Week 0	861.15 (679.98-1213.75)	910.65 (728.9-1231.65)	0.23
0-24 week change	-310 (-485.25--125.75)[a]	-355.5 (-583.4--221.35)[a]	0.09
0-48 week change	-337.4 (-514.8--185.15)[a]	-407.1 (-628.4--252.5)[a]	0.05
sTNF-RI, pg/mL			
Week 0	1186 (948.5-1476.5)	1172.5 (1017-1361)	0.9
0-24 week change	-54 (-227.5-17)[a]	-103 (-215.5--6)[a]	0.28
0-48 week change	-120.5 (-230-16.5)[a]	-123 (-247.5--30)[a]	0.47
IL-6, pg/mL			
Week 0	1.695 (1.205-2.475)	1.715 (1.27-2.765)	0.6
0-24 week change	-0.205 (-0.905-0.185)[a]	-0.34 (-1.05-0.085)[a]	0.55
0-48 week change	-0.27 (-0.935-0.135)[a]	-0.365 (-1.2-0.14)[a]	0.53
hsCRP, ng/mL			
Week 0	1479 (506.5-4977)	1562.5 (751-3209.5)	0.85
0-24 week change	**-108 (-1755-637.7)**	**49.6 (-830-1793)**	**0.04**
0-48 week change	**-176.5 (-1872.5-860.5)[a]**	**55 (-662.5-1759.5)**	**<0.01**
Lp-PLA$_2$, ng/mL			
Week 0	171 (128.5-199)	158 (134.5-188)	0.24
0-24 week change	**-2 (-33-12)[a]**	**4.5 (-19-21)**	**0.02**
0-48 week change	**-6 (-30.5-22.5)**	**9 (-12-26.5)[a]**	**<0.01**
Weight, kg			
0-24 week change	**0.9 (-0.9-3.6)[a]**	**0 (-1.9-2.3)**	**0.01**
0-48 week change	1 (-1.8-5)[a]	0.7 (-2.8-3.1)	0.13
eGFR, mL/min			
0-24 week change	**-11.3 (-22.1--4)[a]**	**-0.2 (-9.8-9.7)**	**<0.0001**
0-48 week change	**-15 (-24.4--2.3)[a]**	**-3.2 (-11.8-8.1)**	**<0.0001**
Glucose, mg/dL			
0-24 week change	2 (-5-9)	5.5 (-1-11.5)[a]	0.06
0-48 week change	**2 (-6-10)**	**5 (-1-11)[a]**	**0.02**
HDL-cholesterol, mg/dL			
0-24 week change	6 (-2-13)[a]	7 (2-13)[a]	0.23
0-48 week change	5 (-2-12)[a]	8 (3-14)[a]	0.05
CD4+ count, cells/mm^3			
0-24 week change	185 (106-271)[a]	155 (73-255)[a]	0.24
0-48 week change	246 (136-358)[a]	217 (124-320)[a]	0.23
HIV-1 RNA <50 copies/mL			
By week 24	95 (95)	96 (96)	0.72

Continuous variables reported as median (IQR) and categorical variables as frequency (percent)

[a] p<0.05 within-group

Changes in hemoglobin, total cholesterol, LDL-cholesterol and triglyceride levels were similar between groups

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



P-values shown are for comparisons between-groups for 0-24 and 0-48 week % changes, respectively. Error bars shown are the IQR. After adjustment for 0-48 week % changes weight, CD4+ count, hemoglobin, eGFR, glucose and lipoprotein levels, 0-48 week % changes in sCD14 and Lp-PLA$_2$ remained significantly different between groups with changes favoring EVG/c/FTC/TDF.

Factors Independently Associated with % Change Over 48 Weeks in sCD14 and Lp-PLA$_2$

Variable	Parameter Estimate (Standard Error)	p
0-48 week % change in log-sCD14[a]		
Randomization group	-2.02x10^{-2} (3.05x10^{-3})	<0.0001
Baseline log-sCD14, ng/mL	-5.44x10^{-2} (6.14x10^{-3})	<0.0001
Baseline log-CD4 count, cells/mm3	6.3x10^{-3} (2.45x10^{-3})	0.01
Baseline log-HDL-cholesterol, mg/dL	1.04x10^{-2} (5.26x10^{-3})	0.05
0-48 week % change log-weight, %	-0.313 (0.104)	<0.01
0-48 week % change log-eGFR, %	-0.109 (5.03x10^{-2})	0.03
0-48 week % change log-sCD163, %	0.1 (2.99x10^{-2})	<0.01
0-48 week % change log-hsCRP, %	3.11x10^{-2} (7.45x10^{-3})	<0.0001
0-48 week % change in Lp-PLA$_2$[b]		
Randomization group	-2.64x10^{-2} (2.56x10^{-2})	0.3
Baseline Lp-PLA$_2$, ng/mL	-1.87x10^{-3} (2.24x10^{-4})	<0.0001
Baseline LDL-cholesterol, mg/dL	1.23x10^{-3} (4.85x10^{-4})	0.01
Baseline IL-6, pg/mL	-2.56x10^{-3} (1.16x10^{-3})	0.03
0-48 week % change total cholesterol, %	0.169 (6.54x10^{-2})	0.01
0-48 week % change triglycerides, %	5.33x10^{-2} (1.85x10^{-2})	<0.01
0-48 week % change sCD14, %	0.229 (6.19x10^{-2})	<0.001
0-48 week % change in sCD163, %	-0.122 (5.4x10^{-2})	0.02

Variables considered: all listed baseline variables as well as 0-48 week % changes in weight, CD4+ count, hemoglobin, eGFR, glucose, lipoprotein levels and other markers of monocyte activation and inflammation

[a]A larger decrease in sCD14 was associated with randomization to EVG/c/FTC/TDF, higher sCD14, lower CD4+ count, lower HDL, larger increases in weight and eGFR, and larger decreases in sCD163 and hsCRP.

[b]A larger decrease in Lp-PLA$_2$ was associated with higher Lp-PLA$_2$ and IL-6, and lower LDL, smaller increases in total cholesterol and triglycerides, larger decrease in sCD14 and smaller decrease in sCD163. After removing changes in sCD14 and sCD163 from the model, randomization group was associated with changes in Lp-PLA$_2$, suggesting monocyte activation may be in the causal pathway.

CONCLUSIONS:

- Antiretroviral initiation with EVG/c/FTC/TDF led to greater decreases in sCD14, hsCRP and Lp-PLA$_2$ than did treatment with EFV/FTC/TDF.
- There were no differences in changes in IL-6, sTNF-RI or sCD163 between-groups.
- 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.

LIMITATIONS:

- Changes in markers were evaluated over a relatively short time. Although inflammation and immune activation likely improve most dramatically in the first year after antiretroviral initiation, longer follow-up would provide additional information as marker levels after suppressive ART are still higher than expected for HIV-uninfected individuals.[4]
- Results may not be generalizable to unboosted integrase inhibitor-based regimens.

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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).