Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Plasma lipidomic profiling

Plasma levels of lipid metabolites were profiled from stored frozen plasma specimens that had been collected at the core study visit closest to the baseline carotid artery imaging study visit, using liquid chromatography-tandem mass spectrometry (LC-MS) at Broad Institute. LC-MS data were acquired using a Nexera X2 U-HPLC (Shimadzu Corp.; Marlborough, MA) coupled to an Exactive Plus mass spectrometer (Thermo Fisher Scientific; Waltham, MA). Lipid metabolites were extracted from plasma (10 µL) using 190 µL of isopropanol containing 1,2-didodecanoyl-sn-glycero-3-phosphocholine (Avanti Polar Lipids; Alabaster, AL). After centrifugation, supernatants were injected directly onto a 100 x 2.1 mm, 1.7 µm ACQUITY BEH C8 column (Waters; Milford, MA). The column was eluted isocratically with 80% mobile phase A (95:5:0.1 vol/vol/vol 10mM ammonium acetate/methanol/formic acid) for 1 minute followed by a linear gradient to 80% mobile-phase B (99.9:0.1 vol/vol methanol/formic acid) over 2 minutes, a linear gradient to 100% mobile phase B over 7 minutes, then 3 minutes at 100% mobile-phase B. MS analyses were carried out using electrospray ionization in the positive ion mode using full scan analysis over 200–1100 m/z at 70,000 resolution and 3 Hz data acquisition rate. Other MS settings were: sheath gas 50, in source CID 5 eV, sweep gas 5, spray voltage 3 kV, capillary temperature 300°C, S-lens RF 60, heater temperature 300°C, microscans 1, automatic gain control target 1e6, and maximum ion time 100 ms. Lipid identities were denoted by total acyl carbon number and total number of double bond number. Raw data were processed using TraceFinder software (Thermo Fisher Scientific; Waltham, MA) and Progenesis QI (Nonlinear Dynamics; Newcastle upon Tyne, UK).

eTable 1. Number of lipid species in each of lipid classes/sub-classes

Lipid classes/sub-classes	Number of lipid species
Cholesterol ester (CE)	13
Diacylglycerol (DAG)	15
Lysophosphatidylcholine (LPC)	10
Lysophosphatidylethanolamine (LPE)	8
Monoacylglycerol (MAG)	4
Phosphatidylcholine (PC)	23
Phosphatidylcholine plasmalogen (PC-P) [a]	15
Phosphatidylethanolamine (PE)	12
Phosphatidylethanolamine plasmalogen (PE-P) [a]	12
Phosphatidylinositol (PI)	2
Phosphatidylserine (PS)	4
Phosphatidylserine plasmalogen (PS-P) [a]	3
Sphingolipid (SL) [b]	
Ceramide (CER) [b]	4
Sphingomyelin (SM) [b]	11
Sphingosine (SS) [b]	1
Triacylglycerol (TAG)	74
All lipid species	211

[a] PC-P, PE-P, and PS-P lipid sub-classes were included into PE, PC and PS lipid classes, respectively.

[b] CER, SM and SS lipid sub-classes were combined into the sphingolipid (SL) lipid class.

CE, cholesteryl ester; CER, ceramide; DAG, diacylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; MAG, monoacylglycerol; PC, phosphatidylcholine; PC-P, phosphatidylcholine plasmalogen; PE, phosphatidylethanolamine; PE-P, phosphatidylethanolamine plasmalogen; PI, phosphatidylinositol; PS, phosphatidylserine; PS-P, phosphatidylserine plasmalogen; SM, sphingomyelin; SS, sphingosine; TAG, triacylglycerol.

eTable 2. Associations of traditional blood lipids with risk of carotid artery plaque

Traditional lipids	Overall samples (n=737)			Non lipid-lowering medication use (n=658)	
	RR (95% CI)	*P*-value		RR (95% CI)	*P*-value
Triglycerides	1.22 (1.03-1.45)	0.02		1.31 (1.09-1.58)	0.005
HDL-cholesterol	0.96 (0.81-1.15)	0.66		0.89 (0.73-1.08)	0.24
LDL-cholesterol	1.15 (0.99-1.33)	0.07		1.21 (1.02-1.44)	0.03
Total-cholesterol	1.23 (1.06-1.43)	0.006		1.25 (1.05-1.50)	0.01

Data were risk ratios (RRs) and 95% confident intervals (CIs) for 1-SD increment of traditional lipids on risk of carotid artery plaque, adjusted for age, sex, race/ethnicity, education, study site, current smoking, HIV serostatus, ART use, CD4+ T-cell count, history of crack cocaine use in past 6 months, History of injected drug use in past 6 months, Hepatitis C serostatus, viral load group.

eTable 3. Conditional analysis results in the PC and PE lipid classes.

Lipid species		r	Primary analysis			Conditional analysis		
			RR (%95 CI)	Raw *P*-values	FDR *P*-values	RR (%95 CI)	Raw *P*-values	FDR *P*-values
Top PC	PC (34:0)	0.41	1.41 (1.20, 1.67)	< 0.001	0.003	1.67 (1.39, 2.01)	< 0.001	< 0.001
Secondary PC	PC (36:4)		0.86 (0.73, 1.01)	0.07	0.11	0.69 (0.59, 0.82)	< 0.001	0.001
Top PE	PE (38:6)	-0.012	1.38 (1.17, 1.63)	< 0.001	0.005	1.40 (1.18, 1.65)	< 0.001	0.002
Secondary PE	PE (P-36:2)		1.27 (1.08, 1.48)	0.003	0.02	1.28 (1.09, 1.50)	0.001	0.05

Correlation coefficients (r) between top and secondary lipid species in the same lipid class were estimated by Spearman correlation analysis. Risk ratios (RRs) and 95% confidence intervals (CIs) of carotid artery plaque per SD increment of lipid species were estimated adjusting for age, sex, race/ethnicity, education, study site and current smoking. Primary analysis included one lipid species in the model. Conditional analysis included both top and secondary lipid species from the same lipid class in the model. PC indicates phosphatidylcholine; PE, phosphatidylethanolamine.

eTable 4. Associations between 12 lipid species and risk of carotid artery plaque among HIV-infected individuals stratified by ART use

Lipid species	ART users (n=406)		ART non-users (n=114)		
	RR (95%CI)	*P*-value	RR (95%CI)	*P*-value	*P* for interaction
CE(16:1)					
Model 1	1.22 (1.01-1.47)	0.04	1.60 (0.99-2.56)	0.05	0.35
Model 2	1.31 (1.05-1.63)	0.02	2.89 (1.27-6.57)	0.01	0.28
CER(16:0)					
Model 1	1.40 (1.10-1.79)	0.006	1.44 (0.76-2.73)	0.26	0.27
Model 2	1.32 (0.95-1.83)	0.10	1.07 (0.40-2.90)	0.89	0.40
DAG(38:5)					
Model 1	1.31 (1.07-1.62)	0.01	0.95 (0.59-1.51)	0.82	0.13
Model 2	1.31 (0.95-1.79)	0.10	0.88 (0.41-1.89)	0.74	0.32
LPC(20:4)					
Model 1	1.35 (1.08-1.69)	0.008	1.07 (0.66-1.74)	0.77	0.20
Model 2	1.34 (1.06-1.69)	0.01	1.38 (0.80-2.40)	0.25	0.43
LPE(16:0)					
Model 1	1.36 (1.08-1.71)	0.009	1.09 (0.63-1.90)	0.76	0.41
Model 2	1.24 (0.96-1.61)	0.10	1.86 (0.75-4.62)	0.18	0.63
PC(34:0)					
Model 1	1.34 (1.07-1.69)	0.01	1.39 (0.81-2.38)	0.23	0.60
Model 2	1.24 (0.90-1.71)	0.19	1.47 (0.64-3.38)	0.37	0.63
PE(38:6)					
Model 1	1.35 (1.10-1.66)	0.004	0.89 (0.58-1.37)	0.59	0.10
Model 2	1.36 (1.06-1.75)	0.02	0.70 (0.44-1.13)	0.14	0.18
PI(34:1)					
Model 1	1.11 (0.87-1.41)	0.40	1.28 (0.68-2.40)	0.45	0.59
Model 2	0.96 (0.73-1.27)	0.80	1.23 (0.71-2.13)	0.46	0.58
PS-P(36:3)					
Model 1	1.29 (1.06-1.57)	0.01	1.11 (0.67-1.82)	0.68	0.38
Model 2	1.21 (0.98-1.49)	0.07	1.29 (0.43-3.87)	0.65	0.50
TAG(54:6)					
Model 1	1.45 (1.19-1.76)	< 0.001	1.24 (0.73-2.11)	0.42	0.02
Model 2	1.36 (1.06-1.75)	0.01	2.06 (0.67-6.33)	0.21	0.11
PC(36:4) [a]					
Model 1	0.65 (0.52-0.80)	< 0.001	0.95 (0.54-1.67)	0.87	0.26
Model 2	0.62 (0.50-0.77)	< 0.001	0.82 (0.45-1.48)	0.51	0.60
PE(P-36:2) [a]					
Model 1	1.17 (0.94-1.47)	0.16	1.57 (0.92-2.70)	0.10	0.54
Model 2	1.20 (0.93-1.54)	0.17	1.56 (0.76-3.20)	0.23	0.33

Data are risk ratios (RRs) and 95% confidence intervals (CIs) of incident carotid artery plaque per SD increment of lipid species, adjusted for age, sex, race/ethnicity, education, study site, current smoking, CD4+ T-cell count, HIV-1 viral load, history of crack cocaine use, history of injected drug use and hepatitis C serostatus (Model 1); and further adjusted for systolic blood pressure, HDL-cholesterol, total cholesterol, triglycerides, BMI, anti-hypertensive medication use and lipid lowering medication use (Model 2). [a] Secondary lipid species.

CE, cholesteryl ester; CER, ceramide; DAG, diacylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; TAG, triacylglycerol.

eTable 5. Sensitivity analyses by excluding participants with lipid medication use, with illicit drug use, or with HCV infection

	Crack cocaine non-users		Injected drug non-users		Without HCV infection		Lipid-lowering medication non-users	
	(92/652)		(85/590)		(84/573)		(93/658)	
	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
CE(16:1)								
Model 1	1.23 (1.01-1.49)	0.04	1.29 (1.07-1.56)	0.009	1.34 (1.11-1.61)	0.002	1.16 (0.97-1.39)	0.11
Model 2	1.30 (1.07-1.57)	0.007	1.29 (1.06-1.57)	0.01	1.37 (1.12-1.68)	0.002	1.23 (1.01-1.49)	0.04
CER(16:0)								
Model 1	1.28 (0.98-1.68)	0.07	1.40 (1.16-1.70)	0.001	1.35 (1.12-1.63)	0.002	1.45 (1.19-1.75)	<0.001
Model 2	1.27 (0.99-1.64)	0.06	1.35 (1.04-1.75)	0.02	1.21 (0.95-1.55)	0.12	1.28 (0.98-1.69)	0.07
DAG(38:5)								
Model 1	1.35 (1.01-1.79)	0.04	1.28 (1.05-1.57)	0.01	1.35 (1.11-1.64)	0.002	1.39 (1.14-1.70)	0.001
Model 2	1.29 (0.97-1.72)	0.08	1.27 (0.96-1.68)	0.10	1.35 (1.02-1.80)	0.04	1.37 (1.02-1.82)	0.03
LPC(20:4)								
Model 1	1.26 (1.00-1.58)	0.05	1.33 (1.07-1.67)	0.01	1.47 (1.21-1.79)	<0.001	1.32 (1.06-1.63)	0.01
Model 2	1.37 (1.10-1.71)	0.004	1.31 (1.03-1.68)	0.03	1.44 (1.15-1.80)	0.001	1.28 (1.01-1.61)	0.04
LPE(16:0)								
Model 1	1.25 (1.01-1.56)	0.04	1.40 (1.13-1.74)	0.002	1.47 (1.19-1.82)	<0.001	1.36 (1.12-1.65)	0.002
Model 2	1.36 (1.08-1.71)	0.009	1.34 (1.07-1.68)	0.01	1.40 (1.11-1.75)	0.004	1.25 (1.00-1.56)	0.05
PC(34:0)								
Model 1	1.25 (0.95-1.64)	0.11	1.30 (1.06-1.59)	0.01	1.38 (1.13-1.68)	0.002	1.40 (1.16-1.70)	0.001
Model 2	1.31 (1.00-1.70)	0.05	1.16 (0.88-1.51)	0.29	1.20 (0.92-1.56)	0.18	1.26 (0.96-1.65)	0.10
PE(38:6)								
Model 1	1.29 (1.02-1.61)	0.03	1.35 (1.10-1.64)	0.003	1.37 (1.13-1.66)	0.002	1.31 (1.09-1.57)	0.003
Model 2	1.30 (1.02-1.65)	0.03	1.34 (1.06-1.69)	0.02	1.32 (1.04-1.67)	0.02	1.28 (1.02-1.61)	0.03
PI(34:1)								
Model 1	0.96 (0.75-1.24)	0.75	1.10 (0.89-1.36)	0.37	1.12 (0.91-1.39)	0.29	1.16 (0.94-1.43)	0.18
Model 2	0.99 (0.78-1.25)	0.93	0.94 (0.73-1.21)	0.64	0.93 (0.72-1.19)	0.55	0.96 (0.74-1.23)	0.74
PS-P(36:3)								
Model 1	1.19 (0.96-1.47)	0.12	1.30 (1.06-1.60)	0.01	1.32 (1.07-1.62)	0.008	1.26 (1.03-1.53)	0.02
Model 2	1.21 (1.00-1.48)	0.05	1.22 (0.98-1.51)	0.08	1.22 (0.97-1.52)	0.08	1.19 (0.96-1.47)	0.12
TAG(54:6)								
Model 1	1.30 (1.04-1.62)	0.02	1.34 (1.12-1.62)	0.002	1.37 (1.15-1.64)	0.001	1.38 (1.14-1.66)	0.001
Model 2	1.31 (1.05-1.63)	0.02	1.26 (1.01-1.58)	0.04	1.27 (1.02-1.57)	0.03	1.32 (1.05-1.66)	0.02
PC(36:4) [a]								
Model 1	0.65 (0.53-0.80)	<0.001	0.64 (0.53-0.79)	<0.001	0.65 (0.53-0.79)	<0.001	0.71 (0.58-0.87)	0.001
Model 2	0.62 (0.51-0.75)	<0.001	0.58 (0.47-0.72)	<0.001	0.57 (0.47-0.70)	<0.001	0.65 (0.53-0.80)	<0.001
PE(P-36:2) [a]								
Model 1	1.25 (1.00-1.55)	0.05	1.20 (0.98-1.48)	0.08	1.19 (0.98-1.45)	0.08	1.24 (1.03-1.50)	0.02
Model 2	1.34 (1.09-1.64)	0.005	1.17 (0.93-1.47)	0.17	1.14 (0.92-1.40)	0.23	1.25 (1.00-1.55)	0.05

Data are risk ratios (RRs) and 95% confidence intervals (CIs) of carotid artery plaque per SD increment of lipid species, adjusted for age, sex, race/ethnicity, education, study site, current smoking, HIV serostatus and treatment status (HIV-, HIV+ ART user, HIV+ ART non-user), CD4+ T-cell count, HIV-1 viral load, history of crack cocaine use (if appropriate), history of injected drug use (if appropriate), and hepatitis C serostatus (if appropriate) (Model 1); and further adjusted for systolic blood pressure, HDL-cholesterol, total cholesterol, triglycerides, BMI, anti-hypertensive medication use and lipid lowering medication use (if appropriate) (Model 2). [a] Secondary lipid species.

CE, cholesteryl ester; CER, ceramide; DAG, diacylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; TAG, triacylglycerol.

eTable 6. Associations of 12 carotid artery plaque-associated lipid species with HIV infection and ART use

| Lipid species | HIV+ vs. HIV- | | | | | | | ART users vs. no users in HIV+ | | | | | |
| | Model 1 | | | | Model 2 | | | Model 1 | | | | Model 2 | |
	Beta	SE	*P*-value		Beta	SE	*P*-value	Beta	SE	*P*-value		Beta	SE	*P*-value
CE (16:1)	-0.072	0.081	0.37		-0.090	0.081	0.27	-0.183	0.110	0.10		-0.103	0.112	0.36
CER(16:0)	0.579	0.078	< 0.001		0.579	0.077	< 0.001	0.431	0.100	< 0.001		0.360	0.100	< 0.001
DAG(38:5)	0.514	0.079	< 0.001		0.468	0.077	< 0.001	0.195	0.106	0.07		0.163	0.106	0.13
LPC(20:4)	0.076	0.081	0.35		0.041	0.077	0.60	0.498	0.106	< 0.001		0.435	0.106	< 0.001
LPE(16:0)	0.351	0.080	< 0.001		0.237	0.077	0.002	0.354	0.106	0.001		0.272	0.104	0.009
PC(34:0)	0.288	0.080	< 0.001		0.244	0.080	0.003	0.473	0.105	< 0.001		0.454	0.108	< 0.001
PE(38:6)	0.378	0.080	< 0.001		0.280	0.080	< 0.001	0.204	0.107	0.06		0.158	0.108	0.15
PI(34:1)	0.272	0.080	0.001		0.302	0.077	< 0.001	0.441	0.106	< 0.001		0.436	0.105	< 0.001
PS-P(36:3)	0.257	0.080	0.001		0.248	0.082	0.003	0.167	0.110	0.13		0.257	0.115	0.03
TAG(54:6)	0.441	0.079	< 0.001		0.409	0.077	< 0.001	0.250	0.108	0.02		0.223	0.107	0.04
PC(36:4) [a]	-0.209	0.081	0.01		-0.168	0.078	0.03	0.205	0.105	0.05		0.156	0.105	0.14
PE(P-36:2) [a]	0.036	0.081	0.65		0.048	0.082	0.55	0.185	0.109	0.09		0.239	0.113	0.04

Data are differences (betas and SEs) of inverse normal transformed levels of 12 carotid artery plaque-associated lipid species between HIV+ and HIV- individuals (reference), and between ART users and non-users (reference), respectively, adjusted for age and sex (Model 1); and further adjusted for race/ethnicity, education, study site, current smoking, history of crack cocaine use, history of injected drug use, Hepatitis C serostatus, systolic blood pressure, BMI, anti-hypertensive medication use and lipid lowering medication use (Model 2). [a] Secondary lipid species.

ART, antiretroviral therapy; CE, cholesteryl ester; CER, ceramide; DAG, diacylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; TAG, triacylglycerol.

eTable 7 Risk of carotid artery plaque discrimination and classification

	C-index	C-index change	P-value	Categorical NRI [a]	P-value	Categorical NRI (Cases) [a]	P-value	Categorical NRI (Non-cases) [a]	P-value	Continuous NRI	P-value	IDI	P-value
All participants													
Conventional risk factors [b]	0.708 (0.659-0.756)	Reference		Reference		Reference		Reference		Reference		Reference	
+ previously reported metabolites [c]	0.737 (0.689-0.785)	0.029 (0.002-0.057)	0.04	0.165 (0.041-0.288)	0.01	0.074 (-0.040-0.188)	0.20	0.091 (0.043-0.138)	< 0.001	0.193 (-0.011-0.398)	0.06	0.032 (0.013-0.052)	0.001
Above + currently reported lipid species [d]	0.778 (0.732-0.824)	0.071 (0.032-0.109)	< 0.001	0.250 (0.112-0.387)	< 0.001	0.046 (-0.080-0.173)	0.47	0.203 (0.150-0.257)	< 0.001	0.545 (0.347-0.743)	< 0.001	0.094 (0.060-0.128)	< 0.001
HIV-infected participants													
Conventional risk factors [b]	0.689 (0.632-0.747)	Reference		Reference		Reference		Reference		Reference		Reference	
+ previously reported metabolites [c]	0.732 (0.676-0.788)	0.043 (0.003-0.083)	0.04	0.108 (-0.051-0.266)	0.18	-0.012 (-0.158-0.134)	0.88	0.119 (0.058-0.181)	< 0.001	0.267 (0.036-0.498)	0.02	0.043 (0.017-0.068)	0.001
Above + currently reported lipid species [d]	0.779 (0.725-0.833)	0.090 (0.038-0.141)	0.001	0.275 (0.108-0.441)	0.001	0.058 (-0.094-0.211)	0.45	0.217 (0.149-0.284)	< 0.001	0.496 (0.269-0.724)	< 0.001	0.108 (0.069-0.147)	< 0.001
HIV-uninfected participants													
Conventional risk factors [b]	0.775 (0.679-0.870)	Reference		Reference		Reference		Reference		Reference		Reference	
+ previously reported metabolites [c]	0.784 (0.690-0.877)	0.009 (-0.027-0.045)	0.63	0.094 (-0.114-0.302)	0.37	0.078 (-0.136-0.292)	0.48	0.045 (-0.153-0.244)	0.65	0.033 (-0.048-0.114)	0.43	0.015 (-0.005-0.034)	0.15
Above + currently reported lipid species [d]	0.832 (0.751-0.913)	0.057 (-0.032-0.147)	0.21	0.390 (0.098-0.682)	0.01	0.168 (-0.129-0.466)	0.27	0.000 (-0.282-0.282)	0.99	0.168 (0.073-0.264)	0.001	0.099 (0.025-0.173)	0.01
MACS men													
Conventional risk factors [b]	0.718 (0.649-0.786)	Reference		Reference		Reference		Reference		Reference		Reference	
+ previously reported metabolites [c]	0.734 (0.665-0.802)	0.016 (-0.013-0.045)	0.28	0.004 (-0.100-0.108)	0.94	0.060 (-0.069-0.188)	0.36	0.060 (-0.049-0.168)	0.28	0.000 (-0.069-0.069)	0.99	0.023 (0.004-0.041)	0.02
Above + currently reported lipid species [d]	0.791 (0.730-0.852)	0.073 (0.024-0.1219)	0.003	0.210 (0.088-0.331)	0.001	0.251 (0.084-0.417)	0.003	0.104 (-0.040-0.249)	0.16	0.146 (0.063-0.230)	0.001	0.096 (0.049-0.143)	< 0.001
WIHS women													
Conventional risk factors [b]	0.771 (0.695-0.847)	Reference		Reference		Reference		Reference		Reference		Reference	
+ previously reported metabolites [c]	0.800 (0.733-0.867)	0.029 (-0.012-0.070)	0.16	0.021 (-0.122-0.165)	0.77	0.098 (-0.081-0.276)	0.28	0.000 (-0.166-0.166)	0.99	0.098 (0.031-0.164)	0.004	0.040 (0.003-0.076)	0.03
Above + currently reported lipid species [d]	0.839 (0.773-0.905)	0.068 (0.011-0.126)	0.02	0.189 (-0.001-0.379)	0.05	0.314 (0.115-0.513)	0.002	0.073 (-0.111-0.257)	0.44	0.241 (0.166-0.316)	< 0.001	0.133 (0.067-0.200)	< 0.001

[a] Categorical NRI was calculated according to quartiles of carotid artery plaque risk.

[b] The model of conventional risk factors included age, sex, race/ethnicity, current smoking, HIV serostatus and treatment status (HIV-, HIV+ ART user, HIV+ ART non-user), systolic blood pressure, HDL-cholesterol, total cholesterol, triglycerides, and BMI.

[c] The previously reported metabolites included kynurenic acid, tryptophan, trimethylamine-N-oxide (TMAO), short-chain acylcarnitine score, and CER(16:0).

[d] The currently reported lipid species included CE (16:1), DAG(38:5), LPC(20:4), LPE(16:0), PC(34:0), PE(38:6), PI(34:1), PS-P(36:3), TAG(54:6), PC(36:4), and PE(P-36:2).

C-index indicates concordance index; CE, cholesteryl ester; CER, ceramide; DAG, diacylglycerol; IDI, integrated discrimination improvement; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; NRI, net reclassification improvement; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; TAG, triacylglycerol.

eTable 8. Associations between lipid sub-network modules and risk of carotid artery plaque by the HIV-infection status.

Modules	HIV-infected participants		HIV-uninfected participants		
	RR (95% CI) per SD [a]	*P*-value	RR (95% CI) per SD s[a]	*P*-value	*P* for interaction
Blue	1.24 (1.04,1.47)	0.02	1.58 (1.09,2.31)	0.02	0.37
Pink	1.26 (1.04,1.53)	0.02	2.08 (1.36,3.18)	0.001	0.15
Turquoise	1.28 (1.06,1.55)	0.01	1.04 (0.72,1.51)	0.83	0.61
Green	1.28 (1.05,1.58)	0.02	1.28 (0.88,1.85)	0.19	0.91
Red	1.24 (0.99,1.56)	0.07	1.31 (0.82,2.08)	0.26	0.54
Yellow	1.11 (0.92,1.34)	0.26	1.33 (0.91,1.96)	0.14	0.21
Brown	1.16 (0.97,1.38)	0.11	1.53 (1.03,2.29)	0.04	0.25
Black	1.11 (0.93,1.31)	0.24	1.76 (1.19,2.60)	0.004	0.02
Magenta	1.04 (0.87,1.24)	0.70	0.97 (0.65,1.46)	0.90	0.86

[a] Data are risk ratios (RRs) and 95% confidence intervals (CIs) of incident carotid artery plaque per SD increment of lipid sub-network scores, adjusted for age, sex, race/ethnicity, education, study site and current smoking.

eFigure 1. Coefficient of variations (CVs) and percentage of missing sample size count for 211 lipid species from 16 lipid classes/sub-classes.

Individual lipid species are depicted by filled circles and arranged by lipid class/sub-class in 16 panels according to carbon numbers (X axes) and double bond number (Y axes). Circle color indicated CVs (**A**) and percentage of missing sample size count (**B**), respectively.

CE, cholesteryl ester; CER, ceramide; DAG, diacylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; MAG, monoacylglycerol; PC, phosphatidylcholine; PC-P, phosphatidylcholine plasmalogen; PE, phosphatidylethanolamine; PE-P, phosphatidylethanolamine plasmalogen; PI, phosphatidylinositol; PS, phosphatidylserine; PS-P, phosphatidylserine plasmalogen; SM, sphingomyelin; SS, sphingosine; TAG, triacylglycerol.
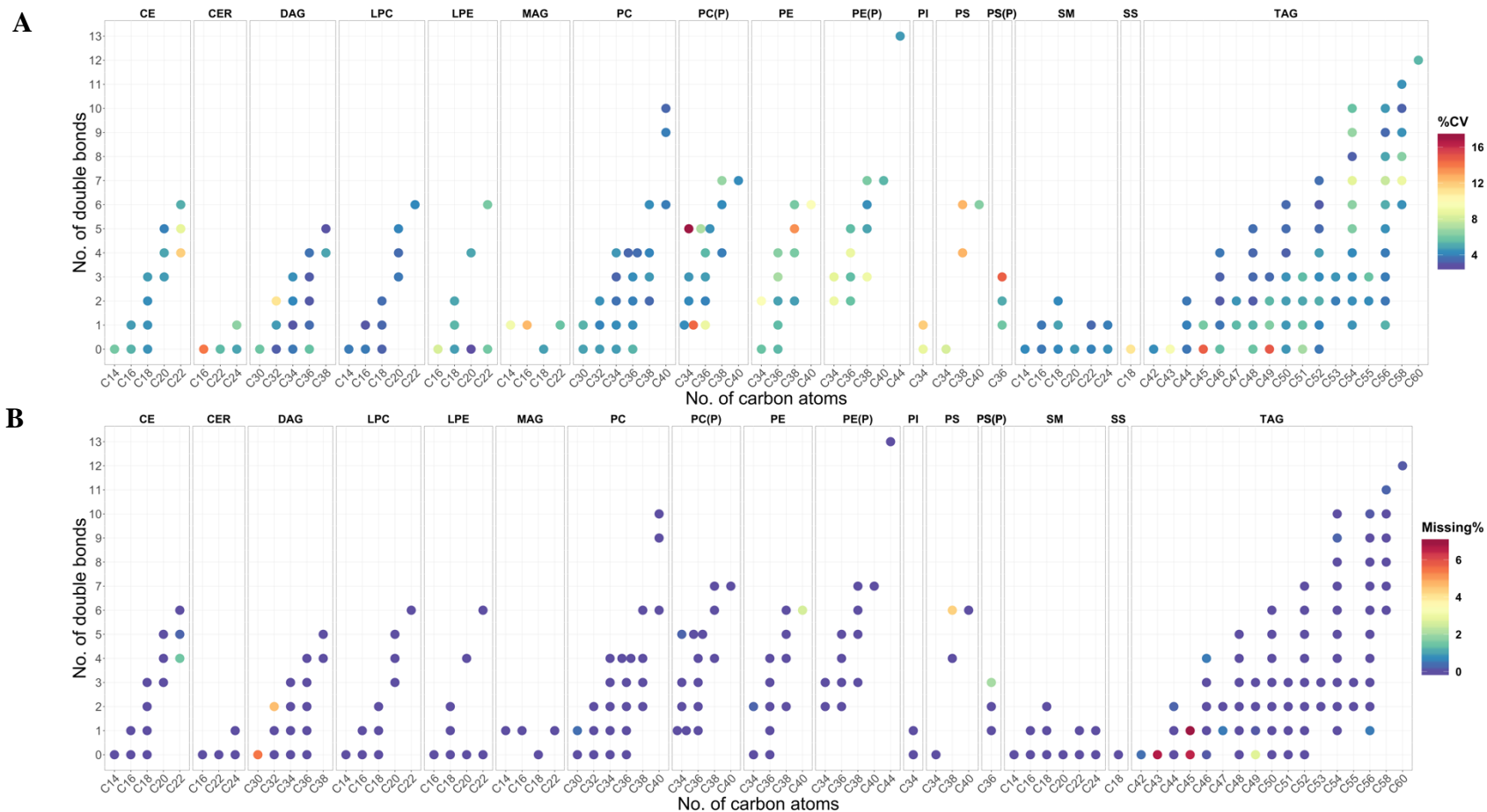
eFigure 2. Pairwise correlation heatmap of 211 individual lipid species in 11 lipid classes.
CE, cholesteryl ester; DAG, diacylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; MAG, monoacylglycerol; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; SL, sphingolipid (include Ceramides (CER), Sphingomyelin (SM), and Sphingosine (SS)), TAG, triacylglycerol.
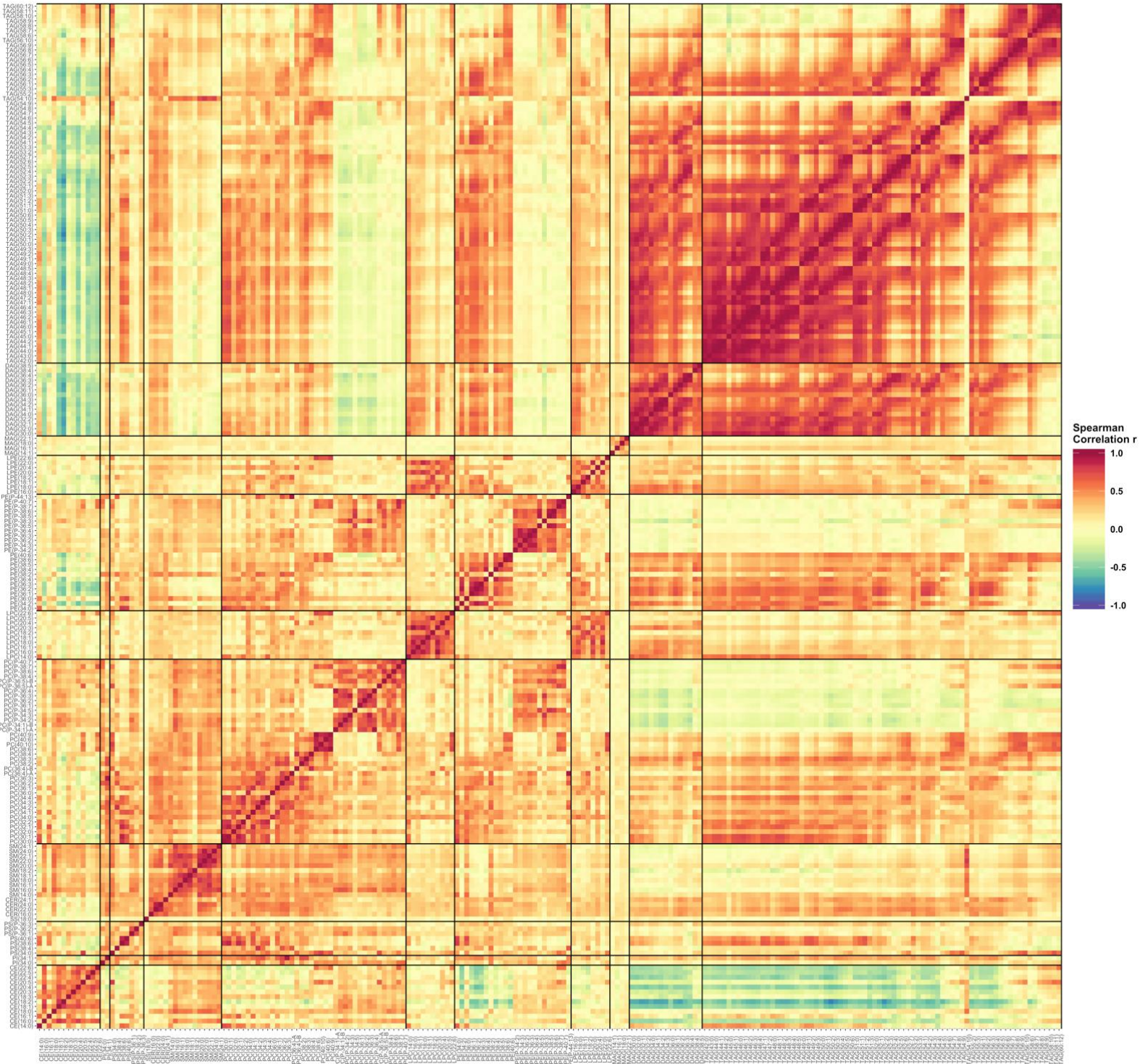
eFigure 3. Plasma levels of carotid artery associated lipid species according to HIV infection and classes of ART use.

Data are inverse normal transformed levels of 12 carotid artery associated lipid species in HIV-uninfected participants (group 0), HIV-infected participants without ART subclass use (group 1), and HIV-infected participants with ART subclass use (group 2). A, B, and C represent PI, NNRTI, and NRTI subclass, respectively.
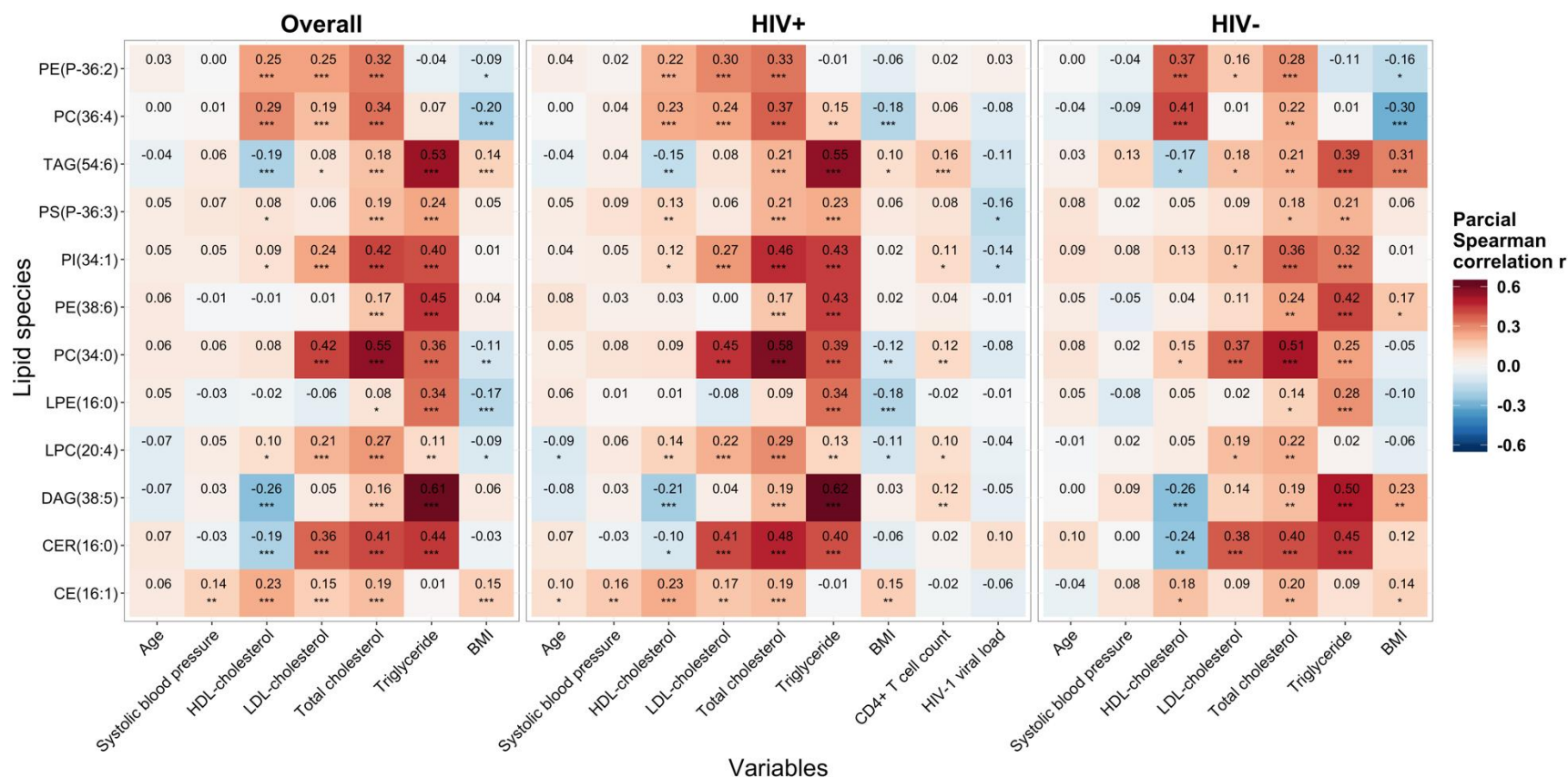
ART, antiretroviral therapy; CE, cholesteryl ester; CER, ceramide; DAG, diacylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; MAG, monoacylglycerol; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; TAG, triacylglycerol.
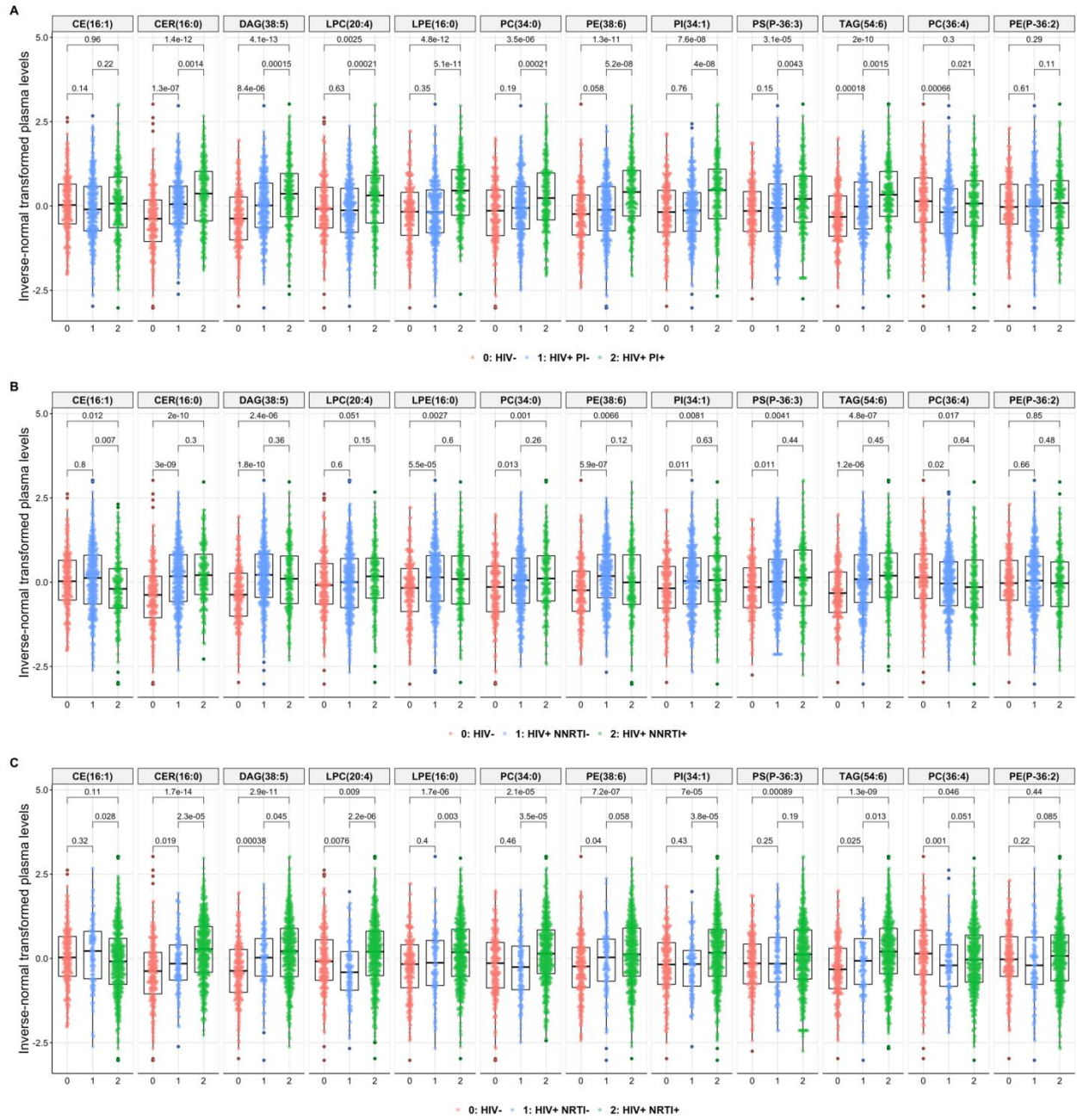
eFigure 4. Partial Spearman correlation of carotid artery plaque associated lipid species with CVD and HIV related factors.

Data are partial Spearman correlation coefficients (r) of 12 carotid artery plaque associated lipid species with age (n=520 HIV+ and 217 HIV- participants), systolic blood pressure (n=433 HIV+ and 186 HIV- participants; participants taking anti-hypertensive medication were excluded), levels of HDL and total cholesterol (n=436 HIV+ and 193 HIV- participants; participants taking lipid-lowering medication were excluded), and BMI (n=520 HIV+ and 216 HIV- participants), baseline CD4+ T cell count (n=520 HIV+ participants) and HIV-1 viral load (n = 234 HIV+ participants with detectable viral load), adjusting for age and sex. *P< 0.05; **P<0.01; ***P<0.001.

CE, cholesteryl ester; CER, ceramide; DAG, diacylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; MAG, monoacylglycerol; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; TAG, triacylglycerol.

eFigure 5. Lipid network with blue and pink sub-network modules
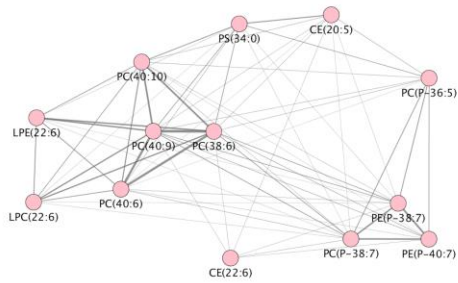
The nodes are individual lipid species and the edges indicate the weighted correlation coefficients between each of lipid species. A total of 9 lipid sub-network modules indicated by different colors (black, blue, brown, green, magenta, pink, red, turquoise, and yellow) were detected by topological overlap measure (**A**). Pink and Blue modules represent the strongest associations with carotid artery plaque (**B** and **C**, respectively).

CE indicates cholesteryl ester; DAG, diacylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; TAG, triacylglycerol.
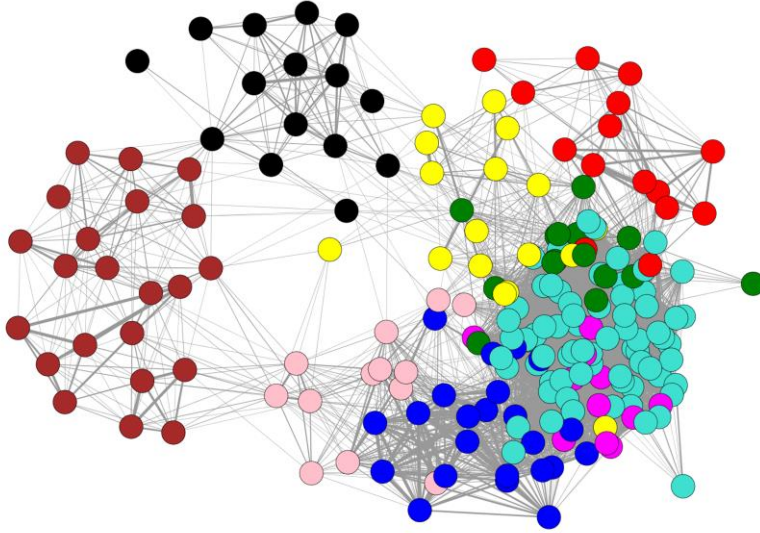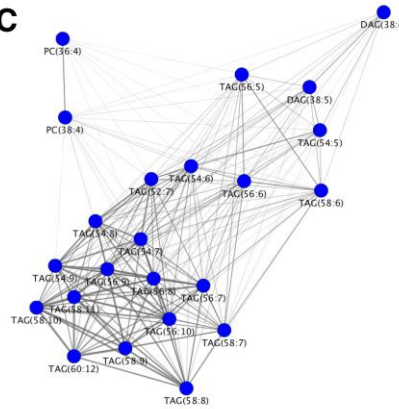
eFigure 6. Associations of 211 individual lipid species with risk of carotid artery plaque according to numbers of carbon atoms and double bond contents.

Individual lipids species are depicted by filled circles and arranged by lipid classes/subclasses in 16-panel columns according to the number of total carbon atoms (x axes) and number of double bonds (y axes). Data are risk ratios (RRs) and P-values of incident carotid artery plaque per 1 SD increment of lipid species, adjusted for age, sex, race/ethnicity, education, study site and current smoking.

CE, cholesteryl ester; CER, ceramide; DAG, diacylglycerol; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; MAG, monoacylglycerol; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; SM, Sphingomyelin; SS, Sphingosine, TAG, triacylglycerol; (P) indicates plasmalogen.