Supplemental Methods:

Metabolomic profiling

Metabolomic profiling was performed by Metabolon (Durham, NC) as previously described [1, 2] using ultra high performance liquid chromatography and tandem mass spectrometry (UHLC/MS/MS2) and gas chromatography (GC)/MS. CSF samples were extracted using the automated MicroLab STAR® system Hamilton Company, Salt Lake City, Utah), divided into two fractions for UHLC/MS/MS2 and GC/MS analysis, placed briefly on a TurboVap® (Zymark), and then frozen and vacuum dried. LC/MS extracts were reconstituted in acidic (eluted using water and methanol both containing 0.1% Formic acid) or basic conditions (eluted using water and methanol containing 6.5mM Ammonium Bicarbonate) and run on a Waters ACQUITY UPLC and a Thermo-Finnigan LTQ mass spectrometer, which consisted of an electrospray ionization (ESI) source and linear ion-trap (LIT) mass analyzer. The MS analysis alternated between MS and data-dependent MS^2 scans using dynamic exclusion. GC/MS samples were re-dried under vacuum desiccation for a minimum of 24 hours, derivatized under dried nitrogen using bistrimethyl-silyl-triflouroacetamide (BSTFA), run on 5% phenyl column (temperature ramp from 40° to 300° C in 16 minutes), and analyzed on a Thermo-Finnigan Trace DSQ fast-scanning single-quadrupole mass spectrometer using electron impact ionization. For quality assurance (QA) and quality control (QC) purposes, additional samples are included in each day’s analysis including two matrix samples (one of pooled human plasma and one of pooled CSF from study samples), an aliquot of pure water, and an aliquot of each solvent used in the extraction. A selection of QC compounds was also added to every sample including a derivatization standard, an internal standard, and a recovery standard. Raw MS data files were loaded into a relational database, examined, and appropriate QC limits imposed. Peaks were identified using Metabolon's proprietary peak integration software, and compounds were identified by comparison to library entries (>1000 compounds) of purified standards or recurrent unknown entities. The combination of chromatographic properties and mass spectra gave an indication of a match to the specific compound or an isobaric entity. Unnamed metabolites were identified by virtue of their recurrent nature (both chromatographic and mass spectral). Quality control and curation processes were performed to ensure accurate and consistent identification of true chemical entities, and to remove those representing system artifacts, misassignments, and background noise using a proprietary visualization and interpretation software.

Neurocognitive testing

All HIV subjects were administered a comprehensive test battery designed to assess neurocognitive function as previously described [3]. Tests were identical for all CHARTER and NNTC sites. Seven categories of neurocognitive function were tested including motor skills (Grooved Pegboard Test, dominant and nondominant hand performances), SIP (WAIS-III Digit Symbol and Symbol Search subtests and Trail Making Test Part A), attention (WAIS-III Letter-Number Sequencing, PASAT-50), learning (Hopkins Verbal Learning Test - Revised, Total Trial 1–3 Recall and Brief Visuospatial Memory Test–Revised), memory (HVLT-R Delayed Recall, BVMI-R Delayed Recall), language fluency (Controlled Oral Word Association Test), and executive function (Wisconsin Card Sorting Test, perseverative responses and TMT Part B). This battery was designed to be brief and repeatable to facilitate multiple assessments over a relatively brief time. Performance on each test generated a raw score, which was converted to a demographically corrected T score as previously described [3]. T scores were then grouped by cognitive domain, and a global T score was generated from the individual T scores. T scores correlate negatively with severity of neurocognitive impairment, with values <40 signifying impairment.

References

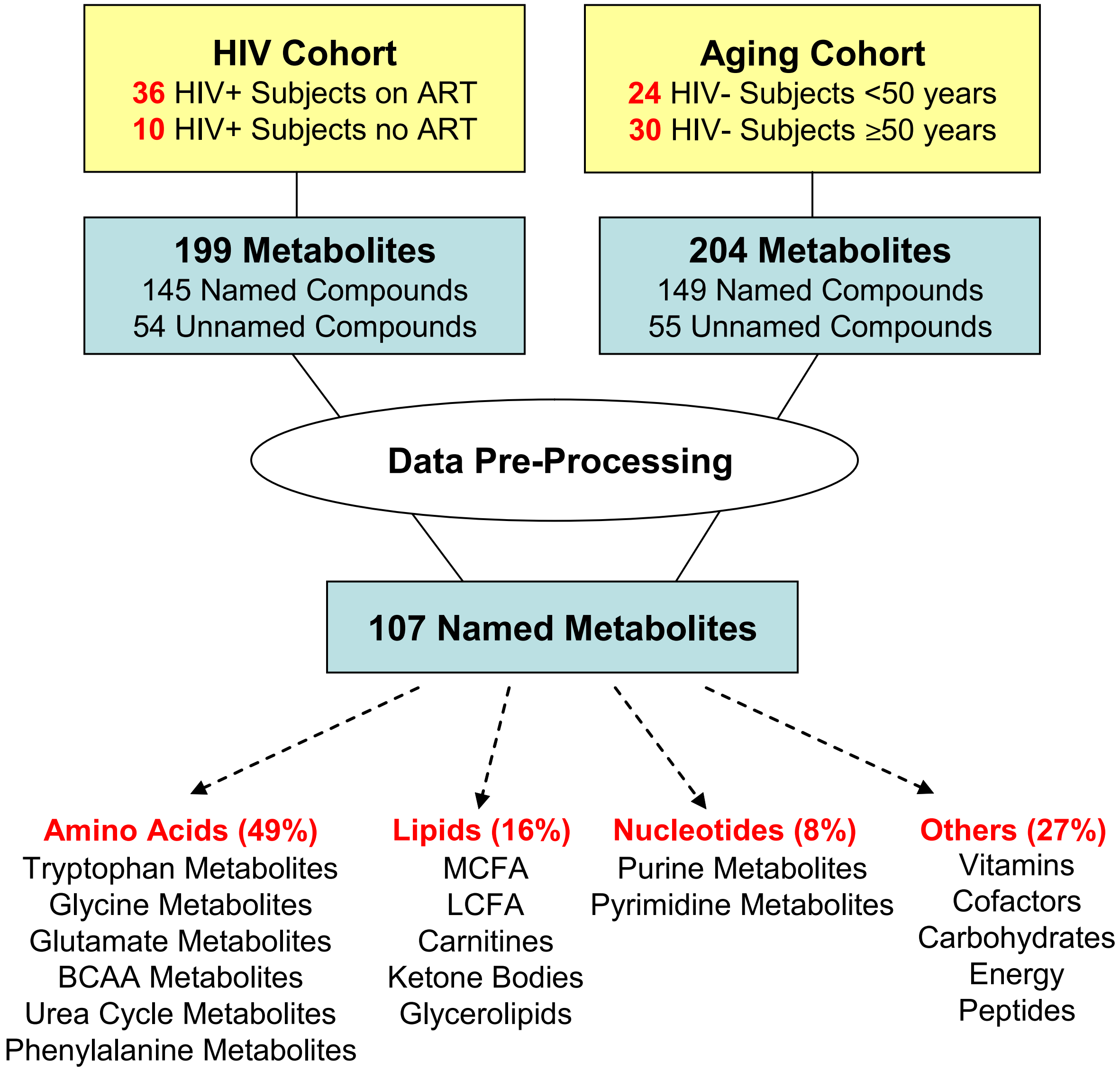
1. Cassol E, Misra V, Holman A, Kamat A, Morgello S, Gabuzda D. Plasma metabolomics identifies lipid abnormalities linked to markers of inflammation, microbial translocation, and hepatic function in HIV patients receiving protease inhibitors. *BMC Infect Dis* 2013,**13**:203.
2. Evans AM, DeHaven CD, Barrett T, Mitchell M, Milgram E. Integrated, nontargeted ultrahigh performance liquid chromatography/electrospray ionization tandem mass spectrometry platform for the identification and relative quantification of the small-molecule complement of biological systems. *Anal Chem* 2009,**81**:6656-6667.
3. Woods SP, Rippeth JD, Frol AB, Levy JK, Ryan E, Soukup VM, *et al*. Interrater reliability of clinical ratings and neurocognitive diagnoses in HIV. *J Clin Exp Neuropsychol* 2004,**26**:759-778.

Supplemental Digital Content 2. Clinical and demographic characteristics of HIV subjects in study cohorts

		HIV on ART (n=36)	**HIV no ART (n=10)**
Demographics	Age (years)*	45 (41-50)	44 (39-49)
	Gender (male)	86%	60%
	Race (African American)	53%	40%
	HCV co-infection (seropositive)	66%	63%
ART Class	Protease Inhibitor Based	72%	0%
	NNRTI Based	28%	0%
	D-drug	31%	0%
Clinical Parameters - HIV	CD4 T-cell count (cells/ul)*	141 (39-287)	70 (23-218)
	Nadir CD4 T-cell count (cells/ul)*	30 (7-90)	34 (11-153)
	Plasma HIV RNA (copies/ml)*	268 (50-11730)	76937 (31725-678174)
	Plasma HIV RNA <400 copies/ml	56%	0%
	CSF HIV RNA (copies/ml)*	50 (50-196)	328 (87-8761)
	CSF HIV RNA <50 copies/ml	83%	10%
HAND Diagnosis	No NCI	33%	30%
	ANI	25%	0%
	MND	14%	10%
	HAD	17%	20%
	NPI-O	11%	30%
	Unable to assign	0%	10%
Neurocognitive Test Scores	Global T*	43 (35-49)	41 (37-46)
	Motor T*	38 (31-49)	33 (29-45)
	SIP T*	45 (36-54)	46 (42-49)
	Memory-encoding T*	40 (28-48)	37 (31-42)
	Memory-retrieval T*	42 (28-52)	38 (27-44)
	Fluency T*	49 (42-56)	47 (37-56)
	Executive Function T*	44 (38-50)	42 (38-47)

Supplemental Digital Content 3

Supplemental Digital Content 3 (Figure). Untargeted metabolite profiling of CSF from 100 HIV and control subjects detected over 200 metabolites. Schematic of strategy used to identify CSF metabolites altered in the HIV and Aging cohorts. BCAA, branched chain amino acids; MCFA, medium chain fatty acids; LCFA, long chain fatty acids.

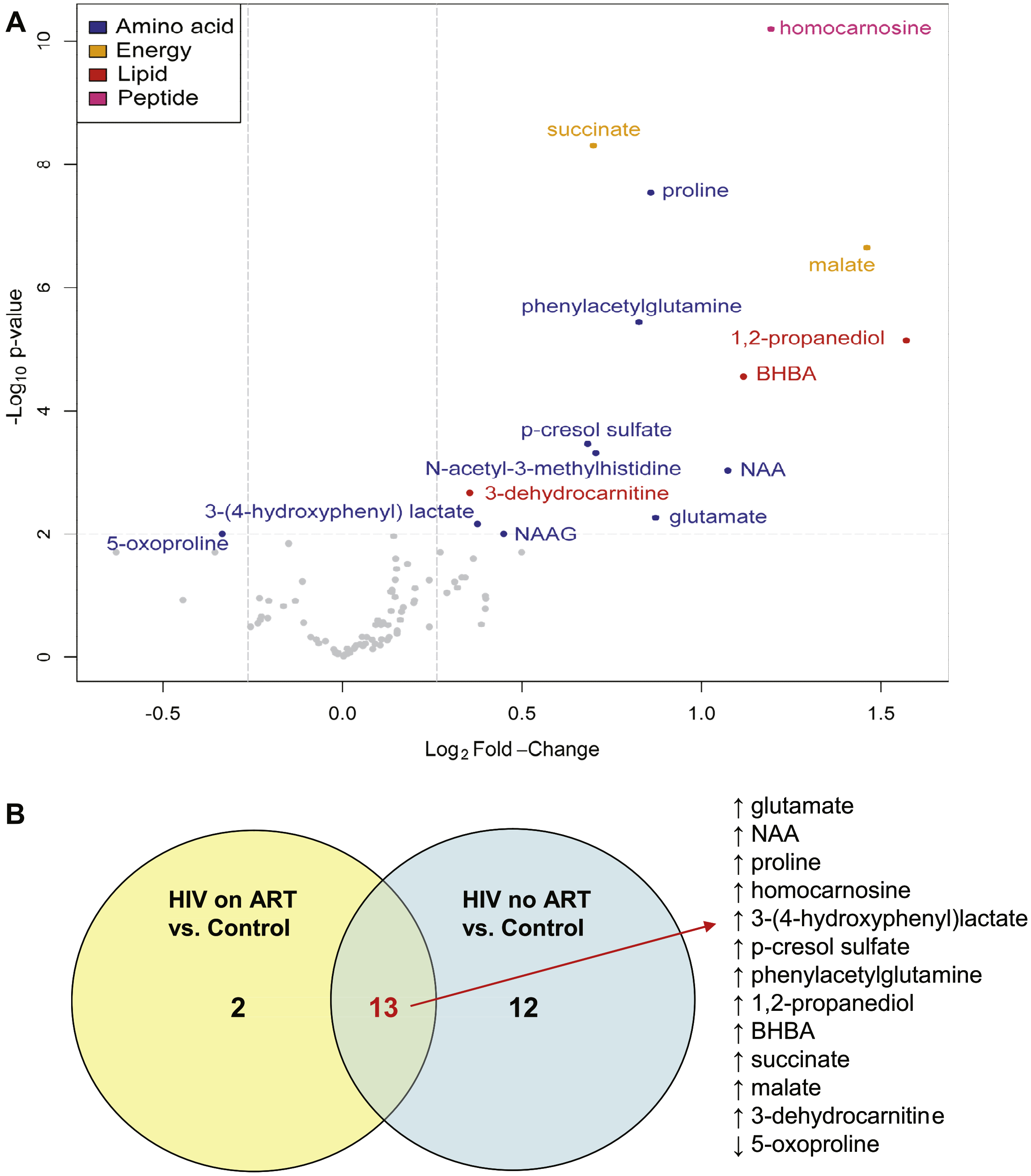


Supplemental Digital Content 4. Alterations in the CSF metabolome of HIV patients on ART compared to HIV-negative controls matched by age and gender. Shown is the total dataset of metabolites detected across HIV and Aging cohorts following data pre-processing. Significantly altered metabolites were defined by a fold change (FC) >1.2, p-value <0.01 and FDR≤0.1.

BIOCHEMICAL	SUPER_PATHWAY	SUB_PATHWAY	FC	p-value	q-value
3-ureidopropionate	Amino acid	Alanine and aspartate metabolism	-1.18	0.281	0.286
alanine	Amino acid	Alanine and aspartate metabolism	1.08	0.274	0.282
asparagine	Amino acid	Alanine and aspartate metabolism	1.11	0.374	0.348
N-acetylalanine	Amino acid	Alanine and aspartate metabolism	1.11	0.052	0.094
N-acetylaspartate (NAA)	Amino acid	Alanine and aspartate metabolism	2.10	0.001	0.004
2-aminobutyrate	Amino acid	Butanoate metabolism	-1.17	0.111	0.154
creatine	Amino acid	Creatine metabolism	1.01	0.733	0.511
creatinine	Amino acid	Creatine metabolism	-1.01	0.862	0.552
2-hydroxybutyrate (AHB)	Amino acid	Cysteine, methionine, SAM, taurine metabolism	-1.16	0.232	0.254
methionine	Amino acid	Cysteine, methionine, SAM, taurine metabolism	-1.08	0.059	0.103
glutamate	Amino acid	Glutamate metabolism	1.83	0.005	0.017
glutamine	Amino acid	Glutamate metabolism	1.12	0.184	0.216
N-acetyl-aspartyl-glutamate (NAAG)	Amino acid	Glutamate metabolism	1.37	0.015	0.039
5-oxoproline	Amino acid	Glutathione metabolism	-1.26	0.014	0.037
betaine	Amino acid	Glycine, serine and threonine metabolism	1.15	0.011	0.032
glycine	Amino acid	Glycine, serine and threonine metabolism	1.12	0.249	0.265
N-acetylserine	Amino acid	Glycine, serine and threonine metabolism	1.10	0.087	0.133
N-acetylthreonine	Amino acid	Glycine, serine and threonine metabolism	1.04	0.467	0.400
serine	Amino acid	Glycine, serine and threonine metabolism	1.08	0.302	0.301
threonine	Amino acid	Glycine, serine and threonine metabolism	1.04	0.655	0.483
4-acetamidobutanoate	Amino acid	Guanidino and acetamido metabolism	1.11	0.106	0.150
N-acetyl-3-methylhistidine	Amino acid	Histidine metabolism	1.63	<0.001	<0.001
lysine	Amino acid	Lysine metabolism	-1.17	0.246	0.263
3-(4-hydroxyphenyl)lactate	Amino acid	Phenylalanine & tyrosine metabolism	1.30	0.007	0.023
p-cresol sulfate	Amino acid	Phenylalanine & tyrosine metabolism	1.61	<0.001	<0.001
phenol sulfate	Amino acid	Phenylalanine & tyrosine metabolism	1.18	0.324	0.316
phenylacetylglutamine	Amino acid	Phenylalanine & tyrosine metabolism	1.77	<0.001	<0.001
phenylalanine	Amino acid	Phenylalanine & tyrosine metabolism	-1.08	0.276	0.283
tyrosine	Amino acid	Phenylalanine & tyrosine metabolism	1.07	0.302	0.301
5-methylthioadenosine (MTA)	Amino acid	Polyamine metabolism	-1.28	0.017	0.042
5-hydroxyindoleacetate	Amino acid	Tryptophan metabolism	1.09	0.532	0.432
C-glycosyltryptophan*	Amino acid	Tryptophan metabolism	1.10	0.088	0.134
kynurenine	Amino acid	Tryptophan metabolism	1.06	0.748	0.516
tryptophan	Amino acid	Tryptophan metabolism	-1.01	0.819	0.539
tryptophan betaine	Amino acid	Tryptophan metabolism	1.11	0.411	0.370
arginine	Amino acid	Urea cycle; arginine-, proline-, metabolism	1.07	0.255	0.270
dimethylarginine (SDMA + ADMA)	Amino acid	Urea cycle; arginine-, proline-, metabolism	1.02	0.687	0.495
proline	Amino acid	Urea cycle; arginine-, proline-, metabolism	1.81	<0.001	<0.001
trans-4-hydroxyproline	Amino acid	Urea cycle; arginine-, proline-, metabolism	1.32	0.112	0.155
urea	Amino acid	Urea cycle; arginine-, proline-, metabolism	-1.05	0.598	0.461
3-hydroxy-2-ethylpropionate	Amino acid	Valine, leucine and isoleucine metabolism	-1.55	0.016	0.040
3-hydroxyisobutyrate	Amino acid	Valine, leucine and isoleucine metabolism	1.01	0.861	0.551
3-methyl-2-oxobutyrate	Amino acid	Valine, leucine and isoleucine metabolism	-1.19	0.014	0.037
3-methyl-2-oxovalerate	Amino acid	Valine, leucine and isoleucine metabolism	-1.06	0.470	0.402
4-methyl-2-oxopentanoate	Amino acid	Valine, leucine and isoleucine metabolism	-1.12	0.149	0.188
alpha-hydroxyisovalerate	Amino acid	Valine, leucine and isoleucine metabolism	-1.17	0.221	0.246
beta-hydroxyisovalerate	Amino acid	Valine, leucine and isoleucine metabolism	-1.01	0.873	0.555
isobutyrylcarnitine	Amino acid	Valine, leucine and isoleucine metabolism	-1.15	0.121	0.162
isoleucine	Amino acid	Valine, leucine and isoleucine metabolism	1.05	0.606	0.464
leucine	Amino acid	Valine, leucine and isoleucine metabolism	-1.01	0.827	0.542
N-acetylvaline	Amino acid	Valine, leucine and isoleucine metabolism	1.04	0.653	0.483
valine	Amino acid	Valine, leucine and isoleucine metabolism	1.00	0.962	0.579
erythronate*	Carbohydrate	Aminosugars metabolism	-1.03	0.551	0.440
N-acetylneuraminate	Carbohydrate	Aminosugars metabolism	1.12	0.157	0.195
1,3-dihydroxyacetone	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	-1.36	0.118	0.159
1,5-anhydroglucitol (1,5-AG)	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	1.07	0.613	0.467
glycerate	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	1.03	0.625	0.472
lactate	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	1.11	0.025	0.053
pyruvate	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	1.32	0.165	0.201
arabinose	Carbohydrate	Nucleotide sugars, pentose metabolism	1.10	0.082	0.129
arabitol	Carbohydrate	Nucleotide sugars, pentose metabolism	-1.01	0.900	0.562
gluconate	Carbohydrate	Nucleotide sugars, pentose metabolism	-1.19	0.323	0.316
ribitol	Carbohydrate	Nucleotide sugars, pentose metabolism	-1.01	0.890	0.560
threitol	Carbohydrate	Nucleotide sugars, pentose metabolism	1.15	0.133	0.173
xylitol	Carbohydrate	Nucleotide sugars, pentose metabolism	1.08	0.643	0.479
xylonate	Carbohydrate	Nucleotide sugars, pentose metabolism	-1.05	0.521	0.427
xylose	Carbohydrate	Nucleotide sugars, pentose metabolism	1.26	0.051	0.093
arabonate	Cofactors and vitamins	Ascorbate and aldarate metabolism	1.09	0.303	0.302
threonate	Cofactors and vitamins	Ascorbate and aldarate metabolism	1.21	0.017	0.042
pantothenate	Cofactors and vitamins	Pantothenate and CoA metabolism	1.22	0.091	0.137
citrate	Energy	Krebs cycle	-1.10	0.122	0.162
malate	Energy	Krebs cycle	2.75	<0.001	<0.001
succinate	Energy	Krebs cycle	1.62	<0.001	<0.001
succinylcarnitine	Energy	Krebs cycle	-1.01	0.899	0.562
3-dehydrocarnitine*	Lipid	Carnitine metabolism	1.28	0.002	0.008
acetylcarnitine	Lipid	Carnitine metabolism	1.32	0.102	0.147
carnitine	Lipid	Carnitine metabolism	-1.02	0.753	0.518
propionylcarnitine	Lipid	Fatty acid metabolism (also BCAA metabolism)	1.24	0.030	0.061
3-hydroxypropanoate	Lipid	Fatty acid, monohydroxy	1.25	0.075	0.121
choline	Lipid	Glycerolipid metabolism	1.02	0.742	0.514
glycerol	Lipid	Glycerolipid metabolism	1.01	0.868	0.553
glycerol 3-phosphate (G3P)	Lipid	Glycerolipid metabolism	1.41	0.015	0.039
myo-inositol	Lipid	Inositol metabolism	1.15	0.119	0.160
1,2-propanediol	Lipid	Ketone bodies	2.97	<0.001	<0.001
3-hydroxybutyrate (BHBA)	Lipid	Ketone bodies	2.17	<0.001	<0.001
acetoacetate	Lipid	Ketone bodies	1.11	0.037	0.073
arachidonate (20:4n6)	Lipid	Long chain fatty acid	1.08	0.518	0.425
caprylate (8:0)	Lipid	Medium chain fatty acid	1.27	0.050	0.091
1-stearoylglycerol (1-monostearin)	Lipid	Monoacylglycerol	1.31	0.293	0.295
7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	Lipid	Sterol/Steroid	1.06	0.524	0.428
hypoxanthine	Nucleotide	Purine metabolism, (hypo)xanthine/inosine containing	1.18	0.056	0.099
inosine	Nucleotide	Purine metabolism, (hypo)xanthine/inosine containing	1.10	0.179	0.213
xanthine	Nucleotide	Purine metabolism, (hypo)xanthine/inosine containing	1.13	0.031	0.063
adenine	Nucleotide	Purine metabolism, adenine containing	1.29	0.025	0.053
N6-carbamoylthreonyladenosine	Nucleotide	Purine metabolism, guanine containing	1.15	0.077	0.123
urate	Nucleotide	Purine metabolism, urate metabolism	1.05	0.470	0.402
cytidine	Nucleotide	Pyrimidine metabolism, cytidine containing	1.01	0.892	0.560
pseudouridine	Nucleotide	Pyrimidine metabolism, uracil containing	1.03	0.642	0.478
uridine	Nucleotide	Pyrimidine metabolism, uracil containing	1.00	0.922	0.568
cyclo(leu-pro)	Peptide	Dipeptide	1.09	0.470	0.402
homocarnosine	Peptide	Dipeptide derivative	2.29	<0.001	<0.001
X - 03056	unnamed		1.05	0.555	0.442
X - 08893	unnamed		-2.67	<0.001	<0.001
X - 11396	unnamed		-1.01	0.942	0.574
X - 11564	unnamed		1.02	0.788	0.529
X - 11593	unnamed		1.08	0.174	0.209
X - 11687	unnamed		1.00	0.957	0.577
X - 11787	unnamed		1.19	0.005	0.017
X - 11977	unnamed		1.88	<0.001	<0.001
X - 12048	unnamed		24.73	<0.001	<0.001
X - 12100	unnamed		-1.14	0.195	0.225
X - 12364	unnamed		1.24	0.024	0.052

X - 12741	unnamed		2.50	0.013	0.035
X - 12776	unnamed		1.04	0.231	0.253
X - 12944	unnamed		-1.03	0.726	0.509
X - 12957	unnamed		1.04	0.703	0.501
X - 14007	unnamed		32.00	<0.001	<0.001
X - 14015	unnamed		6.46	<0.001	<0.001
X - 14588	unnamed		1.03	0.278	0.284
X - 14659	unnamed		1.04	0.636	0.476
X - 15562	unnamed		1.16	0.374	0.348
X - 15563	unnamed		1.23	0.156	0.194
X - 15664	unnamed		-1.10	0.497	0.415
X - 15824	unnamed		11.99	<0.001	<0.001
X - 15825	unnamed		7.39	<0.001	<0.001
X - 16103	unnamed		1.02	0.660	0.485
X - 16206	unnamed		1.04	0.109	0.153
X - 16271	unnamed		1.56	0.024	0.052
X - 16693	unnamed		-1.00	0.972	0.581
X - 16932	unnamed		-1.13	0.379	0.351
X - 16938	unnamed		-1.03	0.747	0.516
X - 17299	unnamed		1.04	0.688	0.496
X - 17564	unnamed		1.00	0.984	0.584
X - 17762	unnamed		1.02	0.467	0.400
X - 18153	unnamed		3.65	<0.001	<0.001
X - 18554	unnamed		2.17	<0.001	<0.001
X - 18638	unnamed		1.29	<0.001	<0.001
X - 19437	unnamed		1.15	0.025	0.053

Supplemental Digital Content 5 (Figure). Metabolites altered in the CSF metabolome of HIV subjects on ART compared to HIV-negative controls. A) Volcano plot of metabolites altered (FC<1.2, p<0.01, FDR<10%) in HIV subjects on ART (n = 36) compared to age- and gender-matched HIV-negative controls (n=36). B) Venn diagram depicting overlap between CSF metabolites altered (FC<1.2, p<0.05, FDR<10%) in HIV subjects on ART (n=36) vs. HIV subjects not on ART (n=10).



Supplemental Digital Content 6. Alterations in the CSF metabolome of HIV patient
CSF VL<50 copies/ml) compared to HIV-negative controls matched by age and gen
pre-processing. Significantly altered metabolites were defined by a fold change (FC)

BIOCHEMICAL	SUPER_PATHWAY
3-ureidopropionate	**Amino acid**
alanine	**Amino acid**
asparagine	**Amino acid**
N-acetylalanine	**Amino acid**
N-acetylaspartate (NAA)	**Amino acid**
2-aminobutyrate	**Amino acid**
creatine	**Amino acid**
creatinine	**Amino acid**
2-hydroxybutyrate (AHB)	**Amino acid**
methionine	**Amino acid**
glutamate	**Amino acid**
glutamine	**Amino acid**
N-acetyl-aspartyl-glutamate (NAAG)	**Amino acid**
5-oxoproline	**Amino acid**
betaine	**Amino acid**
glycine	**Amino acid**
N-acetylserine	**Amino acid**
N-acetylthreonine	**Amino acid**
serine	**Amino acid**
threonine	**Amino acid**
4-acetamidobutanoate	**Amino acid**
N-acetyl-3-methylhistidine*	**Amino acid**
lysine	**Amino acid**
3-(4-hydroxyphenyl)lactate	**Amino acid**
p-cresol sulfate	**Amino acid**
phenol sulfate	**Amino acid**
phenylacetylglutamine	**Amino acid**
phenylalanine	**Amino acid**
tyrosine	**Amino acid**
5-methylthioadenosine (MTA)	**Amino acid**
5-hydroxyindoleacetate	**Amino acid**
C-glycosyltryptophan*	**Amino acid**
kynurenine	**Amino acid**
tryptophan	**Amino acid**
tryptophan betaine	**Amino acid**
arginine	**Amino acid**
dimethylarginine (SDMA + ADMA)	**Amino acid**
proline	**Amino acid**
trans-4-hydroxyproline	**Amino acid**
urea	**Amino acid**
3-hydroxy-2-ethylpropionate	**Amino acid**
3-hydroxyisobutyrate	**Amino acid**
3-methyl-2-oxobutyrate	**Amino acid**

3-methyl-2-oxovalerate	Amino acid
4-methyl-2-oxopentanoate	Amino acid
alpha-hydroxyisovalerate	Amino acid
beta-hydroxyisovalerate	Amino acid
isobutyrylcarnitine	Amino acid
isoleucine	Amino acid
leucine	Amino acid
N-acetylvaline	Amino acid
valine	Amino acid
erythronate*	Carbohydrate
N-acetylneuraminate	Carbohydrate
fructose	Carbohydrate
mannitol	Carbohydrate
mannose	Carbohydrate
sorbitol	Carbohydrate
1,3-dihydroxyacetone	Carbohydrate
1,5-anhydroglucitol (1,5-AG)	Carbohydrate
glucose	Carbohydrate
glycerate	Carbohydrate
lactate	Carbohydrate
pyruvate	Carbohydrate
arabinose	Carbohydrate
arabitol	Carbohydrate
gluconate	Carbohydrate
ribitol	Carbohydrate
threitol	Carbohydrate
xylitol	Carbohydrate
xylonate	Carbohydrate
xylose	Carbohydrate
arabonate	Cofactors and vitamins
threonate	Cofactors and vitamins
pantothenate	Cofactors and vitamins
citrate	Energy
malate	Energy
succinate	Energy
succinylcarnitine	Energy
3-dehydrocarnitine*	Lipid
acetylcarnitine	Lipid
carnitine	Lipid
propionylcarnitine	Lipid
3-hydroxypropanoate	Lipid
choline	Lipid
glycerol	Lipid
glycerol 3-phosphate (G3P)	Lipid
myo-inositol	Lipid
1,2-propanediol	Lipid
3-hydroxybutyrate (BHBA)	Lipid
acetoacetate	Lipid
arachidonate (20:4n6)	Lipid
caproate (6:0)	Lipid
caprylate (8:0)	Lipid

1-stearoylglycerol (1-monostearin)	**Lipid**
7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	**Lipid**
hypoxanthine	**Nucleotide**
inosine	**Nucleotide**
xanthine	**Nucleotide**
adenine	**Nucleotide**
N6-carbamoylthreonyladenosine	**Nucleotide**
urate	**Nucleotide**
cytidine	**Nucleotide**
pseudouridine	**Nucleotide**
uridine	**Nucleotide**
cyclo(leu-pro)	**Peptide**
homocarnosine	**Peptide**

s on stable ART (>2 years on ART) with maximally suppressed viral loads (n=10, plasma VL<50 copies/ml, der (n=10). Shown is the total dataset of metabolites detected across HIV and Aging cohorts following data >1.2, p-value <0.01 and FDR ≤0.1.

SUB_PATHWAY	FC	p-value	q-value
Alanine and aspartate metabolism	1.09	0.584	0.456
Alanine and aspartate metabolism	1.07	0.657	0.485
Alanine and aspartate metabolism	1.13	0.577	0.453
Alanine and aspartate metabolism	1.14	0.075	0.154
Alanine and aspartate metabolism	2.16	0.080	0.157
Butanoate metabolism	-1.37	0.103	0.175
Creatine metabolism	-1.10	0.027	0.101
Creatine metabolism	1.10	0.287	0.323
Cysteine, methionine, SAM, taurine metabolism	-1.22	0.423	0.383
Cysteine, methionine, SAM, taurine metabolism	-1.21	0.017	0.076
Glutamate metabolism	1.93	0.007	0.043
Glutamate metabolism	1.27	0.242	0.296
Glutamate metabolism	1.91	0.068	0.148
Glutathione metabolism	-1.54	0.023	0.092
Glycine, serine and threonine metabolism	1.21	0.065	0.146
Glycine, serine and threonine metabolism	1.21	0.181	0.253
Glycine, serine and threonine metabolism	1.16	0.133	0.208
Glycine, serine and threonine metabolism	-1.01	0.898	0.563
Glycine, serine and threonine metabolism	1.13	0.357	0.356
Glycine, serine and threonine metabolism	-1.22	0.198	0.266
Guanidino and acetamido metabolism	1.23	0.039	0.119
Histidine metabolism	1.67	0.085	0.162
Lysine metabolism	-1.79	0.057	0.139
Phenylalanine & tyrosine metabolism	1.53	0.005	0.035
Phenylalanine & tyrosine metabolism	2.10	0.006	0.042
Phenylalanine & tyrosine metabolism	1.87	0.012	0.061
Phenylalanine & tyrosine metabolism	1.94	0.001	0.009
Phenylalanine & tyrosine metabolism	-1.11	0.450	0.394
Phenylalanine & tyrosine metabolism	1.05	0.723	0.509
Polyamine metabolism	-1.16	0.352	0.353
Tryptophan metabolism	1.16	0.458	0.397
Tryptophan metabolism	1.09	0.431	0.386
Tryptophan metabolism	1.40	0.316	0.337
Tryptophan metabolism	1.04	0.778	0.528
Tryptophan metabolism	1.55	0.057	0.139
Urea cycle; arginine-, proline-, metabolism	-1.19	0.101	0.174
Urea cycle; arginine-, proline-, metabolism	-1.11	0.414	0.379
Urea cycle; arginine-, proline-, metabolism	2.04	<0.001	0.003
Urea cycle; arginine-, proline-, metabolism	-1.01	0.972	0.583
Urea cycle; arginine-, proline-, metabolism	-1.18	0.237	0.294
Valine, leucine and isoleucine metabolism	-1.52	0.254	0.304
Valine, leucine and isoleucine metabolism	-1.06	0.503	0.419
Valine, leucine and isoleucine metabolism	-1.14	0.392	0.369

Valine, leucine and isoleucine metabolism	-1.01	0.918	0.569
Valine, leucine and isoleucine metabolism	1.01	0.912	0.567
Valine, leucine and isoleucine metabolism	-1.01	0.975	0.583
Valine, leucine and isoleucine metabolism	-1.16	0.357	0.355
Valine, leucine and isoleucine metabolism	-1.17	0.321	0.340
Valine, leucine and isoleucine metabolism	-1.12	0.534	0.434
Valine, leucine and isoleucine metabolism	-1.01	0.911	0.567
Valine, leucine and isoleucine metabolism	1.38	0.076	0.155
Valine, leucine and isoleucine metabolism	1.01	0.934	0.573
Aminosugars metabolism	1.02	0.843	0.548
Aminosugars metabolism	1.18	0.277	0.317
Fructose, mannose, galactose, starch, and sucrose metabolism	-1.41	0.100	0.173
Fructose, mannose, galactose, starch, and sucrose metabolism	-1.37	0.361	0.357
Fructose, mannose, galactose, starch, and sucrose metabolism	-1.23	0.041	0.123
Fructose, mannose, galactose, starch, and sucrose metabolism	-1.34	0.041	0.122
Glycolysis, gluconeogenesis, pyruvate metabolism	-1.57	0.113	0.187
Glycolysis, gluconeogenesis, pyruvate metabolism	1.12	0.670	0.491
Glycolysis, gluconeogenesis, pyruvate metabolism	-1.30	0.031	0.108
Glycolysis, gluconeogenesis, pyruvate metabolism	-1.05	0.666	0.489
Glycolysis, gluconeogenesis, pyruvate metabolism	1.16	0.089	0.165
Glycolysis, gluconeogenesis, pyruvate metabolism	1.45	0.391	0.369
Nucleotide sugars, pentose metabolism	1.18	0.140	0.216
Nucleotide sugars, pentose metabolism	-1.04	0.810	0.538
Nucleotide sugars, pentose metabolism	-1.17	0.564	0.448
Nucleotide sugars, pentose metabolism	-1.17	0.128	0.203
Nucleotide sugars, pentose metabolism	1.05	0.779	0.528
Nucleotide sugars, pentose metabolism	-1.12	0.712	0.505
Nucleotide sugars, pentose metabolism	-1.19	0.211	0.276
Nucleotide sugars, pentose metabolism	-1.02	0.930	0.572
Ascorbate and aldarate metabolism	-1.05	0.822	0.541
Ascorbate and aldarate metabolism	-1.02	0.802	0.535
Pantothenate and CoA metabolism	1.48	0.068	0.148
Krebs cycle	-1.15	0.254	0.304
Krebs cycle	5.13	<0.001	0.002
Krebs cycle	1.77	<0.001	0.003
Krebs cycle	-1.05	0.729	0.512
Carnitine metabolism	1.37	0.057	0.138
Carnitine metabolism	1.11	0.759	0.521
Carnitine metabolism	-1.14	0.271	0.314
Fatty acid metabolism (also BCAA metabolism)	-1.08	0.700	0.502
Fatty acid, monohydroxy	-1.18	0.348	0.352
Glycerolipid metabolism	1.03	0.776	0.527
Glycerolipid metabolism	-1.03	0.780	0.528
Glycerolipid metabolism	1.35	0.159	0.233
Inositol metabolism	1.15	0.298	0.328
Ketone bodies	6.49	<0.001	0.000
Ketone bodies	2.90	<0.001	0.005
Ketone bodies	1.20	0.012	0.061
Long chain fatty acid	-1.08	0.725	0.510
Medium chain fatty acid	-1.12	0.441	0.390
Medium chain fatty acid	-1.16	0.334	0.345

Monoacylglycerol	-1.09	0.868	0.555
Sterol/Steroid	1.20	0.379	0.364
Purine metabolism, (hypo)xanthine/inosine containing	1.30	0.013	0.065
Purine metabolism, (hypo)xanthine/inosine containing	1.13	0.390	0.369
Purine metabolism, (hypo)xanthine/inosine containing	1.25	0.047	0.129
Purine metabolism, adenine containing	1.57	0.029	0.105
Purine metabolism, guanine containing	1.28	0.054	0.136
Purine metabolism, urate metabolism	1.13	0.358	0.356
Pyrimidine metabolism, cytidine containing	-1.05	0.651	0.483
Pyrimidine metabolism, uracil containing	-1.06	0.603	0.464
Pyrimidine metabolism, uracil containing	-1.10	0.195	0.264
Dipeptide	1.14	0.641	0.479
Dipeptide derivative	2.56	<0.001	0.003

Supplemental Digital Content 7. Alterations in the CSF metabolome of HIV patients not on ART (n=10) compared to HIV-negative controls matched by age and gender (n=10). Shown is the total dataset of metabolites detected across HIV and Aging cohorts following data pre-processing. Significantly altered metabolites were defined by a fold change (FC) >1.2, p-value <0.01 and FDR <0.1.

BIOCHEMICAL	SUPER_PATHWAY	SUB_PATHWAY	FC	p-value	q-value
3-ureidopropionate	Amino acid	Alanine and aspartate metabolism	1.37	0.055	0.124
alanine	Amino acid	Alanine and aspartate metabolism	1.18	0.076	0.142
asparagine	Amino acid	Alanine and aspartate metabolism	-1.08	0.862	0.592
N-acetylalanine	Amino acid	Alanine and aspartate metabolism	1.23	0.060	0.129
N-acetylaspartate (NAA)	Amino acid	Alanine and aspartate metabolism	2.17	0.089	0.157
2-aminobutyrate	Amino acid	Butanoate metabolism	-1.01	0.410	0.409
creatine	Amino acid	Creatine metabolism	-1.03	0.263	0.308
creatinine	Amino acid	Creatine metabolism	-1.05	0.971	0.621
2-hydroxybutyrate (AHB)	Amino acid	Cysteine, methionine, SAM, taurine metabolism	1.10	0.773	0.566
methionine	Amino acid	Cysteine, methionine, SAM, taurine metabolism	-1.07	0.191	0.251
glutamate	Amino acid	Glutamate metabolism	3.33	0.003	0.018
glutamine	Amino acid	Glutamate metabolism	-1.04	0.527	0.471
N-acetyl-aspartyl-glutamate (NAAG)	Amino acid	Glutamate metabolism	1.49	0.253	0.301
5-oxoproline	Amino acid	Glutathione metabolism	-1.33	0.046	0.114
betaine	Amino acid	Glycine, serine and threonine metabolism	1.29	0.004	0.021
glycine	Amino acid	Glycine, serine and threonine metabolism	1.27	0.059	0.128
N-acetylserine	Amino acid	Glycine, serine and threonine metabolism	1.35	0.065	0.133
N-acetylthreonine	Amino acid	Glycine, serine and threonine metabolism	1.11	0.388	0.396
serine	Amino acid	Glycine, serine and threonine metabolism	1.13	0.688	0.537
threonine	Amino acid	Glycine, serine and threonine metabolism	-1.09	0.294	0.332
4-acetamidobutanoate	Amino acid	Guanidino and acetamido metabolism	1.05	0.640	0.519
N-acetyl-3-methylhistidine	Amino acid	Histidine metabolism	1.72	0.290	0.328
lysine	Amino acid	Lysine metabolism	1.17	0.849	0.589
3-(4-hydroxyphenyl)lactate	Amino acid	Phenylalanine & tyrosine metabolism	1.50	0.026	0.083
p-cresol sulfate	Amino acid	Phenylalanine & tyrosine metabolism	1.52	0.047	0.115
phenol sulfate	Amino acid	Phenylalanine & tyrosine metabolism	1.62	0.028	0.087
phenylacetylglutamine	Amino acid	Phenylalanine & tyrosine metabolism	1.69	0.003	0.018
phenylalanine	Amino acid	Phenylalanine & tyrosine metabolism	1.27	0.063	0.131
tyrosine	Amino acid	Phenylalanine & tyrosine metabolism	1.19	0.086	0.153
5-methylthioadenosine (MTA)	Amino acid	Polyamine metabolism	-1.27	0.177	0.240
5-hydroxyindoleacetate	Amino acid	Tryptophan metabolism	1.23	0.203	0.259
C-glycosyltryptophan*	Amino acid	Tryptophan metabolism	1.24	0.108	0.178
kynurenine	Amino acid	Tryptophan metabolism	2.27	0.004	0.021
tryptophan	Amino acid	Tryptophan metabolism	1.09	0.371	0.385
tryptophan betaine	Amino acid	Tryptophan metabolism	1.16	0.364	0.380
arginine	Amino acid	Urea cycle; arginine-, proline-, metabolism	-1.03	0.475	0.445
dimethylarginine (SDMA + ADMA)	Amino acid	Urea cycle; arginine-, proline-, metabolism	1.23	0.076	0.142
proline	Amino acid	Urea cycle; arginine-, proline-, metabolism	2.19	<0.001	<0.001
trans-4-hydroxyproline	Amino acid	Urea cycle; arginine-, proline-, metabolism	1.25	0.363	0.380
urea	Amino acid	Urea cycle; arginine-, proline-, metabolism	1.14	0.201	0.258
3-hydroxy-2-ethylpropionate	Amino acid	Valine, leucine and isoleucine metabolism	1.55	0.401	0.403
3-hydroxyisobutyrate	Amino acid	Valine, leucine and isoleucine metabolism	1.28	0.130	0.199
3-methyl-2-oxobutyrate	Amino acid	Valine, leucine and isoleucine metabolism	-1.45	0.042	0.109
3-methyl-2-oxovalerate	Amino acid	Valine, leucine and isoleucine metabolism	-1.05	0.944	0.614
4-methyl-2-oxopentanoate	Amino acid	Valine, leucine and isoleucine metabolism	-1.17	0.614	0.509
alpha-hydroxyisovalerate	Amino acid	Valine, leucine and isoleucine metabolism	1.27	0.259	0.305
beta-hydroxyisovalerate	Amino acid	Valine, leucine and isoleucine metabolism	-1.06	0.541	0.477
isobutyrylcarnitine	Amino acid	Valine, leucine and isoleucine metabolism	-1.00	0.919	0.608
isoleucine	Amino acid	Valine, leucine and isoleucine metabolism	1.07	0.949	0.615
leucine	Amino acid	Valine, leucine and isoleucine metabolism	1.11	0.400	0.403
N-acetylvaline	Amino acid	Valine, leucine and isoleucine metabolism	1.48	0.123	0.193
valine	Amino acid	Valine, leucine and isoleucine metabolism	1.10	0.372	0.386
erythronate*	Carbohydrate	Aminosugars metabolism	1.11	0.527	0.471
N-acetylneuraminate	Carbohydrate	Aminosugars metabolism	1.34	0.076	0.142
1,3-dihydroxyacetone	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	-1.08	0.593	0.500
1,5-anhydroglucitol (1,5-AG)	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	1.17	0.726	0.550
glycerate	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	1.04	0.921	0.608
lactate	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	1.15	0.011	0.044
pyruvate	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	-1.22	0.385	0.394
arabinose	Carbohydrate	Nucleotide sugars, pentose metabolism	1.17	0.117	0.187
arabitol	Carbohydrate	Nucleotide sugars, pentose metabolism	1.10	0.665	0.529
gluconate	Carbohydrate	Nucleotide sugars, pentose metabolism	-1.38	0.635	0.517
ribitol	Carbohydrate	Nucleotide sugars, pentose metabolism	1.08	0.485	0.450
threitol	Carbohydrate	Nucleotide sugars, pentose metabolism	1.42	0.005	0.023
xylitol	Carbohydrate	Nucleotide sugars, pentose metabolism	1.50	0.102	0.172
xylonate	Carbohydrate	Nucleotide sugars, pentose metabolism	1.04	0.592	0.500
xylose	Carbohydrate	Nucleotide sugars, pentose metabolism	1.33	0.150	0.218
arabonate	Cofactors and vitamins	Ascorbate and aldarate metabolism	1.05	0.971	0.621
threonate	Cofactors and vitamins	Ascorbate and aldarate metabolism	1.01	0.702	0.542
pantothenate	Cofactors and vitamins	Pantothenate and CoA metabolism	1.56	0.005	0.023
citrate	Energy	Krebs cycle	-1.15	0.206	0.261
malate	Energy	Krebs cycle	4.69	<0.001	<0.001
succinate	Energy	Krebs cycle	1.78	<0.001	<0.001
succinylcarnitine	Energy	Krebs cycle	1.17	0.700	0.541
3-dehydrocarnitine*	Lipid	Carnitine metabolism	1.67	0.003	0.018
acetylcarnitine	Lipid	Carnitine metabolism	2.03	0.021	0.072
carnitine	Lipid	Carnitine metabolism	1.16	0.031	0.092
propionylcarnitine	Lipid	Fatty acid metabolism (also BCAA metabolism)	1.50	0.057	0.126
3-hydroxypropanoate	Lipid	Fatty acid, monohydroxy	1.56	0.335	0.361
choline	Lipid	Glycerolipid metabolism	1.47	0.001	0.009
glycerol	Lipid	Glycerolipid metabolism	-1.07	0.469	0.442
glycerol 3-phosphate (G3P)	Lipid	Glycerolipid metabolism	-1.04	0.965	0.619
myo-inositol	Lipid	Inositol metabolism	1.44	0.013	0.051
1,2-propanediol	Lipid	Ketone bodies	3.34	<0.001	<0.001
3-hydroxybutyrate (BHBA)	Lipid	Ketone bodies	2.80	<0.001	<0.001
acetoacetate	Lipid	Ketone bodies	1.02	0.263	0.308
arachidonate (20:4n6)	Lipid	Long chain fatty acid	1.19	0.514	0.464
caprylate (8:0)	Lipid	Medium chain fatty acid	1.35	0.375	0.387
1-stearoylglycerol (1-monostearin)	Lipid	Monoacylglycerol	2.36	0.461	0.437
7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	Lipid	Sterol/Steroid	1.03	0.416	0.412
hypoxanthine	Nucleotide	Purine metabolism, (hypo)xanthine/inosine containing	1.11	0.377	0.389
inosine	Nucleotide	Purine metabolism, (hypo)xanthine/inosine containing	-1.10	0.287	0.326
xanthine	Nucleotide	Purine metabolism, (hypo)xanthine/inosine containing	1.10	0.179	0.242
adenine	Nucleotide	Purine metabolism, adenine containing	1.12	1.000	0.628
N6-carbamoylthreonyladenosine	Nucleotide	Purine metabolism, guanine containing	1.29	0.046	0.114
urate	Nucleotide	Purine metabolism, urate metabolism	1.25	0.039	0.105
cytidine	Nucleotide	Pyrimidine metabolism, cytidine containing	-1.12	0.471	0.443
pseudouridine	Nucleotide	Pyrimidine metabolism, uracil containing	1.15	0.178	0.241
uridine	Nucleotide	Pyrimidine metabolism, uracil containing	-1.06	0.538	0.476
cyclo(leu-pro)	Peptide	Dipeptide	1.40	0.135	0.204
homocarnosine	Peptide	Dipeptide derivative	1.72	0.004	0.021

Supplemental Digital Content 8 Alterations in the HIV CSF metabolome overlap with those associated with normal aging in HIV-negative controls. Shown is fold change analysis of young (< age 50) vs. old (≥ age 50) HIV-negative controls and young HIV (age <50) subjects on ART vs. young HIV-negative controls. Young (n=23) and older (n=23) HIV-negative controls were matched by gender and race. Young HIV
young HIV-negative subjects (n=23) were matched by age and gender. Significantly altered metabolites were defined by a fold change>1.2, p<0.05, and q<0.10.

			Older HIV-negative subjects vs. Young HIV-negative subjects			Young HIV-positive subjects vs. Young HI	
BIOCHEMICAL	SUPER_PATHWAY	SUB_PATHWAY	FC	p-value	q-value	FC	p-value
3-ureidopropionate	Amino acid	Alanine and aspartate metabolism	1.70	0.0078	0.0221	-1.00	0.9975
alanine	Amino acid	Alanine and aspartate metabolism	1.11	0.3728	0.2033	1.12	0.1665
asparagine	Amino acid	Alanine and aspartate metabolism	-1.41	0.0258	0.0410	1.15	0.2911
N-acetylalanine	Amino acid	Alanine and aspartate metabolism	1.19	0.0076	0.0219	1.16	0.0347
N-acetylaspartate (NAA)	Amino acid	Alanine and aspartate metabolism	1.04	0.8707	0.3620	1.56	0.1488
2-aminobutyrate	Amino acid	Butanoate metabolism	1.41	0.0148	0.0300	-1.11	0.3698
creatine	Amino acid	Creatine metabolism	1.05	0.1318	0.1170	1.04	0.3447
creatinine	Amino acid	Creatine metabolism	1.05	0.3889	0.2069	1.06	0.3284
2-hydroxybutyrate (AHB)	Amino acid	Cysteine, methionine, SAM, taurine metabolism	1.72	0.0024	0.0141	1.06	0.6345
methionine	Amino acid	Cysteine, methionine, SAM, taurine metabolism	1.11	0.0560	0.0640	1.02	0.7645
glutamate	Amino acid	Glutamate metabolism	1.71	0.0296	0.0437	2.04	0.0337
glutamine	Amino acid	Glutamate metabolism	-1.23	0.0876	0.0890	1.10	0.1488
N-acetyl-aspartyl-glutamate (NAAG)	Amino acid	Glutamate metabolism	-1.22	0.2814	0.1793	1.05	0.7340
5-oxoproline	Amino acid	Glutathione metabolism	1.48	0.0010	0.0092	-1.20	0.1020
betaine	Amino acid	Glycine, serine and threonine metabolism	1.11	0.1979	0.1490	1.19	0.0321
glycine	Amino acid	Glycine, serine and threonine metabolism	1.13	0.3928	0.2077	1.16	0.1110
N-acetylserine	Amino acid	Glycine, serine and threonine metabolism	1.11	0.1637	0.1332	1.14	0.0557
N-acetylthreonine	Amino acid	Glycine, serine and threonine metabolism	1.23	0.0062	0.0208	1.11	0.2107
serine	Amino acid	Glycine, serine and threonine metabolism	-1.12	0.4070	0.2106	1.07	0.3971
threonine	Amino acid	Glycine, serine and threonine metabolism	-1.12	0.4688	0.2340	1.02	0.8284
4-acetamidobutanoate	Amino acid	Guanidino and acetamido metabolism	1.03	0.6990	0.3130	1.08	0.4452
N-acetyl-3-methylhistidine*	Amino acid	Histidine metabolism	-1.04	0.8386	0.3534	1.16	0.4249
lysine	Amino acid	Lysine metabolism	1.11	0.5639	0.2688	-1.02	0.9350
3-(4-hydroxyphenyl)lactate	Amino acid	Phenylalanine & tyrosine metabolism	1.45	0.0055	0.0200	1.50	0.0012
p-cresol sulfate	Amino acid	Phenylalanine & tyrosine metabolism	1.34	0.1747	0.1385	1.53	0.0133
phenol sulfate	Amino acid	Phenylalanine & tyrosine metabolism	1.47	0.1537	0.1284	1.45	0.0348
phenylacetylglutamine	Amino acid	Phenylalanine & tyrosine metabolism	1.56	0.0153	0.0306	1.80	0.0001
phenylalanine	Amino acid	Phenylalanine & tyrosine metabolism	1.19	0.0783	0.0821	1.00	0.9583
tyrosine	Amino acid	Phenylalanine & tyrosine metabolism	1.04	0.7484	0.3279	1.14	0.0876
5-methylthioadenosine (MTA)	Amino acid	Polyamine metabolism	1.17	0.2082	0.1533	-1.30	0.0443
5-hydroxyindoleacetate	Amino acid	Tryptophan metabolism	1.17	0.3433	0.1964	-1.02	0.8914
C-glycosyltryptophan	Amino acid	Tryptophan metabolism	1.25	0.0070	0.0215	1.13	0.0884
kynurenine	Amino acid	Tryptophan metabolism	1.45	0.1621	0.1324	1.13	0.6118
tryptophan	Amino acid	Tryptophan metabolism	1.03	0.8337	0.3521	1.09	0.2841
tryptophan betaine	Amino acid	Tryptophan metabolism	-1.02	0.9126	0.3730	-1.12	0.5187
arginine	Amino acid	Urea cycle; arginine-, proline-, metabolism	-1.07	0.4254	0.2174	1.12	0.2154
dimethylarginine (SDMA + ADMA)	Amino acid	Urea cycle; arginine-, proline-, metabolism	1.22	0.0096	0.0238	1.07	0.3462
proline	Amino acid	Urea cycle; arginine-, proline-, metabolism	1.16	0.2611	0.1728	2.01	<0.0001
trans-4-hydroxyproline	Amino acid	Urea cycle; arginine-, proline-, metabolism	-1.11	0.6762	0.3059	1.49	0.0908
urea	Amino acid	Urea cycle; arginine-, proline-, metabolism	1.31	0.0227	0.0384	-1.02	0.8522
3-hydroxy-2-ethylpropionate	Amino acid	Valine, leucine and isoleucine metabolism	1.20	0.4461	0.2253	-1.29	0.3110
3-hydroxyisobutyrate	Amino acid	Valine, leucine and isoleucine metabolism	1.32	0.0175	0.0332	1.08	0.4618
3-methyl-2-oxobutyrate	Amino acid	Valine, leucine and isoleucine metabolism	1.09	0.3028	0.1856	-1.13	0.2084
3-methyl-2-oxovalerate	Amino acid	Valine, leucine and isoleucine metabolism	1.26	0.0364	0.0491	1.12	0.1601
4-methyl-2-oxopentanoate	Amino acid	Valine, leucine and isoleucine metabolism	1.25	0.0358	0.0487	-1.02	0.7654
alpha-hydroxyisovalerate	Amino acid	Valine, leucine and isoleucine metabolism	1.27	0.2555	0.1709	1.02	0.9370
beta-hydroxyisovalerate	Amino acid	Valine, leucine and isoleucine metabolism	1.31	0.0281	0.0427	1.09	0.3801
isobutyrylcarnitine	Amino acid	Valine, leucine and isoleucine metabolism	1.27	0.0671	0.0733	1.01	0.9487
isoleucine	Amino acid	Valine, leucine and isoleucine metabolism	1.13	0.3328	0.1937	1.14	0.2138
leucine	Amino acid	Valine, leucine and isoleucine metabolism	1.11	0.2315	0.1624	1.04	0.5989
N-acetylvaline	Amino acid	Valine, leucine and isoleucine metabolism	1.06	0.6042	0.2825	1.17	0.2222
valine	Amino acid	Valine, leucine and isoleucine metabolism	1.08	0.2668	0.1747	1.03	0.6317
erythronate*	Carbohydrate	Aminosugars metabolism	1.23	0.0143	0.0295	-1.02	0.7303
N-acetylneuraminate	Carbohydrate	Aminosugars metabolism	1.19	0.1527	0.1279	1.17	0.1316
1,3-dihydroxyacetone	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	1.14	0.6032	0.2822	-1.40	0.2257
1,5-anhydroglucitol (1,5-AG)	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	-1.13	0.3835	0.2057	-1.03	0.8359
glycerate	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	1.30	0.0037	0.0173	1.12	0.3135
lactate	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	1.19	0.0026	0.0146	1.15	0.0081
pyruvate	Carbohydrate	Glycolysis, gluconeogenesis, pyruvate metabolism	1.06	0.8626	0.3599	1.27	0.3445
arabinose	Carbohydrate	Nucleotide sugars, pentose metabolism	1.23	0.0094	0.0237	1.17	0.0303
arabitol	Carbohydrate	Nucleotide sugars, pentose metabolism	1.25	0.0432	0.0538	-1.00	0.9685
gluconate	Carbohydrate	Nucleotide sugars, pentose metabolism	-1.12	0.6401	0.2944	-1.42	0.1969
ribitol	Carbohydrate	Nucleotide sugars, pentose metabolism	1.22	0.0401	0.0516	1.06	0.5342
threitol	Carbohydrate	Nucleotide sugars, pentose metabolism	1.54	0.0003	0.0074	1.34	0.0253
xylitol	Carbohydrate	Nucleotide sugars, pentose metabolism	1.08	0.6670	0.3030	-1.29	0.1578
xylonate	Carbohydrate	Nucleotide sugars, pentose metabolism	1.43	0.0012	0.0094	1.01	0.9512
xylose	Carbohydrate	Nucleotide sugars, pentose metabolism	1.24	0.1618	0.1323	1.23	0.1634
arabonate	Cofactors and vitamins	Ascorbate and aldarate metabolism	1.17	0.2028	0.1511	1.01	0.9591
threonate	Cofactors and vitamins	Ascorbate and aldarate metabolism	1.17	0.2649	0.1741	1.29	0.0540
pantothenate	Cofactors and vitamins	Pantothenate and CoA metabolism	1.17	0.4000	0.2092	1.14	0.4569
citrate	Energy	Krebs cycle	1.17	0.0567	0.0645	-1.07	0.3466
malate	Energy	Krebs cycle	1.13	0.3699	0.2027	3.08	0.0002
succinate	Energy	Krebs cycle	1.20	0.0460	0.0556	1.69	<0.0001
succinylcarnitine	Energy	Krebs cycle	1.00	0.9786	0.3894	1.05	0.5442
3-dehydrocarnitine	Lipid	Carnitine metabolism	1.11	0.3945	0.2081	1.22	0.0796
acetylcarnitine	Lipid	Carnitine metabolism	-1.06	0.8079	0.3449	1.21	0.4178
carnitine	Lipid	Carnitine metabolism	1.12	0.1089	0.1035	-1.01	0.8407
propionylcarnitine	Lipid	Fatty acid metabolism (also BCAA metabolism)	1.15	0.2673	0.1748	1.36	0.0342
3-hydroxypropanoate	Lipid	Fatty acid, monohydroxy	1.22	0.1500	0.1266	1.07	0.6881
choline	Lipid	Glycerolipid metabolism	1.34	0.0004	0.0074	1.10	0.3043
glycerol	Lipid	Glycerolipid metabolism	1.24	0.2634	0.1736	-1.00	0.9507
glycerol 3-phosphate (G3P)	Lipid	Glycerolipid metabolism	-1.08	0.6945	0.3116	1.28	0.0721
myo-inositol	Lipid	Inositol metabolism	1.05	0.7000	0.3133	1.08	0.4993
1,2-propanediol	Lipid	Ketone bodies	1.88	0.0422	0.0775	4.04	<0.0001
3-hydroxybutyrate (BHBA)	Lipid	Ketone bodies	1.84	0.0402	0.0517	2.38	<0.0001
acetoacetate	Lipid	Ketone bodies	1.10	0.4966	0.2445	1.07	0.2970
arachidonate (20:4n6)	Lipid	Long chain fatty acid	1.53	0.0125	0.0277	1.21	0.1122
caprylate (8:0)	Lipid	Medium chain fatty acid	-1.10	0.2782	0.1783	1.45	0.1015
1-stearoylglycerol (1-monostearin)	Lipid	Monoacylglycerol	-1.65	0.1072	0.1024	1.19	0.6513
7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	Lipid	Sterol/Steroid	1.01	0.9591	0.3847	-1.03	0.7787
hypoxanthine	Nucleotide	Purine metabolism, (hypo)xanthine/inosine containing	1.33	0.0229	0.0385	1.15	0.1997
inosine	Nucleotide	Purine metabolism, (hypo)xanthine/inosine containing	1.11	0.3323	0.1936	1.13	0.1590
xanthine	Nucleotide	Purine metabolism, (hypo)xanthine/inosine containing	1.04	0.5285	0.2562	1.10	0.3103
adenine	Nucleotide	Purine metabolism, adenine containing	-1.08	0.5661	0.2695	1.08	0.6241
N6-carbamoylthreonyladenosine	Nucleotide	Purine metabolism, guanine containing	1.16	0.1617	0.1322	1.17	0.1794
urate	Nucleotide	Purine metabolism, urate metabolism	1.42	0.0043	0.0183	1.24	0.0303
cytidine	Nucleotide	Pyrimidine metabolism, cytidine containing	-1.07	0.3961	0.2084	-1.07	0.5534
pseudouridine	Nucleotide	Pyrimidine metabolism, uracil containing	1.26	0.0009	0.0091	1.08	0.3042
uridine	Nucleotide	Pyrimidine metabolism, uracil containing	-1.06	0.3904	0.2072	-1.07	0.2212
cyclo(leu-pro)	Peptide	Dipeptide	-1.18	0.3258	0.1919	1.02	0.9002
homocarnosine	Peptide	Dipeptide derivative	-1.43	0.0282	0.0428	1.87	0.0005

Supplemental Digital Content 9. Metabolic alterations associated with neurocognitive impairment in HIV subjects on ART. Fold change analysis was performed on a subset of HIV subjects on ART with (n=12) and without NCI (n=14) matched for age, gender, race, current and nadir CD4, and plasma and CSF viral load (plasma VL<1000 copies/ml; CSF VL<50 copies/ml). HIV-negative controls (n=14) were matched for age and gender. Shown is the total dataset of 107 metabolites detected in HIV and Aging Cohorts following data pre-processing. Significantly altered metabolites were defined by a FC>1.2, p<0.05, and q<0.1.

			HIV-positive subjects with NCI vs. HIV-negative subjects			HIV-positive subjects without NCI vs. HIV-negative subjects			HIV-positive subjects with NCI vs. HIV-positive subjects without NCI		
BIOCHEMICAL	**SUPER_PATHWAY**	**SUB_PATHWAY**	**FC**	**p-value**	**q-value**	**FC**	**p-value**	**q-value**	**FC**	**p-value**	**q-value**
3-ureidopropionate	**Amino acid**	**Alanine and aspartate metabolism**	-1.22	0.3220	0.4493	-1.10	0.6811	0.5625	-1.12	0.5609	1.0000
alanine	**Amino acid**	**Alanine and aspartate metabolism**	1.16	0.1448	0.3308	1.17	0.1108	0.3124	-1.01	0.8655	1.0000
asparagine	**Amino acid**	**Alanine and aspartate metabolism**	1.08	0.6424	0.6194	1.06	0.7671	0.5915	1.03	0.8841	1.0000
N-acetylalanine	**Amino acid**	**Alanine and aspartate metabolism**	1.09	0.3027	0.4341	1.02	0.8321	0.6110	1.07	0.4651	1.0000
N-acetylaspartate (NAA)	**Amino acid**	**Alanine and aspartate metabolism**	2.63	0.0157	0.0863	1.70	0.1144	0.3152	1.54	0.2904	1.0000
2-aminobutyrate	**Amino acid**	**Butanoate metabolism**	-1.09	0.6116	0.6078	-1.10	0.5754	0.5207	1.01	0.9244	1.0000
creatine	**Amino acid**	**Creatine metabolism**	1.04	0.3279	0.4538	1.02	0.6575	0.5539	1.03	0.5618	1.0000
creatinine	**Amino acid**	**Creatine metabolism**	1.03	0.6919	0.6368	-1.02	0.6776	0.5613	1.05	0.4844	1.0000
2-hydroxybutyrate (AHB)	**Amino acid**	**Cysteine, methionine, SAM, taurine metabolism**	-1.17	0.4380	0.5260	-1.13	0.5472	0.5082	-1.04	0.7167	1.0000
methionine	**Amino acid**	**Cysteine, methionine, SAM, taurine metabolism**	-1.12	0.1289	0.3162	-1.10	0.1342	0.3283	-1.02	0.7654	1.0000
glutamate	**Amino acid**	**Glutamate metabolism**	3.08	0.0001	0.0023	1.65	0.0833	0.2862	1.86	0.0356	1.0000
glutamine	**Amino acid**	**Glutamate metabolism**	-1.02	0.8312	0.6781	-1.03	0.5036	0.4938	1.01	0.8871	1.0000
N-acetyl-aspartyl-glutamate (NAAG)	**Amino acid**	**Glutamate metabolism**	1.25	0.1646	0.3465	1.16	0.4136	0.4666	1.08	0.5692	1.0000
5-oxoproline	**Amino acid**	**Glutathione metabolism**	-1.02	0.9057	0.6965	-1.21	0.1334	0.3279	1.19	0.2925	1.0000
betaine	**Amino acid**	**Glycine, serine and threonine metabolism**	1.12	0.2776	0.4140	1.10	0.1535	0.3386	1.02	0.8581	1.0000
glycine	**Amino acid**	**Glycine, serine and threonine metabolism**	1.72	0.0010	0.0097	1.39	0.0325	0.1922	1.23	0.0132	1.0000
N-acetylserine	**Amino acid**	**Glycine, serine and threonine metabolism**	1.00	0.9591	0.7085	1.05	0.5817	0.5234	-1.04	0.5656	1.0000
N-acetylthreonine	**Amino acid**	**Glycine, serine and threonine metabolism**	1.03	0.7354	0.6508	-1.05	0.4792	0.4871	1.08	0.3665	1.0000
serine	**Amino acid**	**Glycine, serine and threonine metabolism**	1.05	0.6022	0.6041	-1.07	0.5293	0.5003	1.12	0.1421	1.0000
threonine	**Amino acid**	**Glycine, serine and threonine metabolism**	1.07	0.6516	0.6228	1.07	0.6913	0.5662	1.00	0.9835	1.0000
4-acetamidobutanoate	**Amino acid**	**Guanidino and acetamido metabolism**	1.04	0.7049	0.6411	-1.10	0.3423	0.4384	1.14	0.2224	1.0000
N-acetyl-3-methylhistidine*	**Amino acid**	**Histidine metabolism**	1.47	0.0740	0.2435	1.58	0.0738	0.2743	-1.07	0.6848	1.0000
lysine	**Amino acid**	**Lysine metabolism**	-1.05	0.8280	0.6772	1.18	0.4205	0.4689	-1.24	0.3074	1.0000
3-(4-hydroxyphenyl)lactate	**Amino acid**	**Phenylalanine & tyrosine metabolism**	1.26	0.1004	0.2837	1.23	0.1923	0.3541	1.03	0.8235	1.0000
p-cresol sulfate	**Amino acid**	**Phenylalanine & tyrosine metabolism**	1.53	0.0373	0.1059	1.54	0.0369	0.2016	-1.00	0.9857	1.0000
phenol sulfate	**Amino acid**	**Phenylalanine & tyrosine metabolism**	1.27	0.3769	0.4885	1.18	0.5431	0.5062	1.07	0.5881	1.0000
phenylacetylglutamine	**Amino acid**	**Phenylalanine & tyrosine metabolism**	1.64	0.0114	0.0686	1.44	0.0532	0.2402	1.15	0.3915	1.0000
phenylalanine	**Amino acid**	**Phenylalanine & tyrosine metabolism**	-1.14	0.2305	0.3844	-1.08	0.4378	0.4746	-1.05	0.5026	1.0000
tyrosine	**Amino acid**	**Phenylalanine & tyrosine metabolism**	1.03	0.7367	0.6512	1.08	0.3730	0.4514	-1.05	0.5134	1.0000
5-methylthioadenosine (MTA)	**Amino acid**	**Polyamine metabolism**	-1.11	0.4601	0.5383	-1.26	0.1384	0.3308	1.14	0.3746	1.0000
5-hydroxyindoleacetate	**Amino acid**	**Tryptophan metabolism**	-1.24	0.3730	0.4859	-1.01	0.9554	0.6434	-1.23	0.3684	1.0000
C-glycosyltryptophan*	**Amino acid**	**Tryptophan metabolism**	1.03	0.6792	0.6325	-1.04	0.6966	0.5681	1.07	0.3361	1.0000
kynurenine	**Amino acid**	**Tryptophan metabolism**	1.18	0.5537	0.5838	-1.21	0.4932	0.4910	1.44	0.1665	1.0000
tryptophan	**Amino acid**	**Tryptophan metabolism**	1.01	0.9473	0.7059	1.05	0.6186	0.5387	-1.04	0.6315	1.0000
tryptophan betaine	**Amino acid**	**Tryptophan metabolism**	1.24	0.3471	0.4680	1.31	0.2732	0.4027	-1.06	0.7128	1.0000
arginine	**Amino acid**	**Urea cycle; arginine-, proline-, metabolism**	1.13	0.3330	0.4576	1.20	0.0378	0.2035	-1.06	0.6243	1.0000
dimethylarginine (SDMA + ADMA)	**Amino acid**	**Urea cycle; arginine-, proline-, metabolism**	1.01	0.9009	0.6954	1.09	0.3471	0.4405	-1.08	0.3804	1.0000
proline	**Amino acid**	**Urea cycle; arginine-, proline-, metabolism**	2.02	0.0005	0.0057	1.92	0.0009	0.0160	1.05	0.5788	1.0000
trans-4-hydroxyproline	**Amino acid**	**Urea cycle; arginine-, proline-, metabolism**	1.46	0.1355	0.3225	1.23	0.4090	0.4649	1.18	0.5030	1.0000
urea	**Amino acid**	**Urea cycle; arginine-, proline-, metabolism**	1.03	0.8387	0.6800	-1.06	0.6261	0.5417	1.09	0.5213	1.0000
3-hydroxy-2-ethylpropionate	**Amino acid**	**Valine, leucine and isoleucine metabolism**	-1.42	0.2436	0.3933	-1.41	0.2049	0.3581	-1.01	0.9722	1.0000
3-hydroxyisobutyrate	**Amino acid**	**Valine, leucine and isoleucine metabolism**	1.04	0.8199	0.6751	1.01	0.9582	0.6440	1.03	0.7230	1.0000
3-methyl-2-oxobutyrate	**Amino acid**	**Valine, leucine and isoleucine metabolism**	-1.24	0.0954	0.2770	-1.11	0.2988	0.4171	-1.11	0.3676	1.0000
3-methyl-2-oxovalerate	**Amino acid**	**Valine, leucine and isoleucine metabolism**	-1.08	0.6263	0.6135	-1.03	0.8305	0.6106	-1.05	0.6179	1.0000
4-methyl-2-oxopentanoate	**Amino acid**	**Valine, leucine and isoleucine metabolism**	-1.20	0.1988	0.3683	-1.14	0.3319	0.4336	-1.05	0.5553	1.0000
alpha-hydroxyisovalerate	**Amino acid**	**Valine, leucine and isoleucine metabolism**	-1.05	0.8473	0.6822	-1.23	0.3550	0.4439	1.18	0.2755	1.0000
beta-hydroxyisovalerate	**Amino acid**	**Valine, leucine and isoleucine metabolism**	1.01	0.9442	0.7052	-1.09	0.5240	0.4990	1.10	0.2244	1.0000
isobutyrylcarnitine	**Amino acid**	**Valine, leucine and isoleucine metabolism**	1.02	0.8623	0.6860	-1.25	0.0511	0.2359	1.27	0.0077	1.0000
isoleucine	**Amino acid**	**Valine, leucine and isoleucine metabolism**	1.09	0.4880	0.5529	1.14	0.2212	0.3678	-1.05	0.5939	1.0000
leucine	**Amino acid**	**Valine, leucine and isoleucine metabolism**	-1.02	0.8405	0.6805	1.04	0.6650	0.5567	-1.06	0.4288	1.0000
N-acetylvaline	**Amino acid**	**Valine, leucine and isoleucine metabolism**	1.20	0.2150	0.3770	-1.22	0.1679	0.3450	1.46	0.0058	1.0000
valine	**Amino acid**	**Valine, leucine and isoleucine metabolism**	-1.07	0.4577	0.5370	1.01	0.8977	0.6289	-1.08	0.2316	1.0000
erythronate*	**Carbohydrate**	**Aminosugars metabolism**	-1.09	0.2738	0.4118	-1.12	0.1256	0.3230	1.02	0.7642	1.0000
N-acetylneuraminate	**Carbohydrate**	**Aminosugars metabolism**	-1.02	0.8956	0.6941	-1.08	0.4844	0.4886	1.07	0.5191	1.0000
fructose	**Carbohydrate**	**Fructose, mannose, galactose, starch, and sucrose metabolism**	-1.11	0.2604	0.4039	-1.10	0.3326	0.4340	-1.01	0.8867	1.0000
mannitol	**Carbohydrate**	**Fructose, mannose, galactose, starch, and sucrose metabolism**	-1.22	0.2563	0.4014	-1.45	0.0124	0.1174	1.19	0.3598	1.0000
mannose	**Carbohydrate**	**Fructose, mannose, galactose, starch, and sucrose metabolism**	-1.17	0.0916	0.2717	-1.20	0.0377	0.2032	1.03	0.6967	1.0000
sorbitol	**Carbohydrate**	**Fructose, mannose, galactose, starch, and sucrose metabolism**	-1.19	0.2203	0.3796	-1.16	0.3525	0.4429	-1.03	0.8132	1.0000
1,3-dihydroxyacetone	**Carbohydrate**	**Glycolysis, gluconeogenesis, pyruvate metabolism**	-1.60	0.1838	0.3594	-1.07	0.7665	0.5914	-1.49	0.1878	1.0000
1,5-anhydroglucitol (1,5-AG)	**Carbohydrate**	**Glycolysis, gluconeogenesis, pyruvate metabolism**	1.29	0.1790	0.3563	1.22	0.3277	0.4316	1.06	0.5715	1.0000
glucose	**Carbohydrate**	**Glycolysis, gluconeogenesis, pyruvate metabolism**	-1.07	0.5689	0.5904	-1.15	0.2085	0.3592	1.08	0.4760	1.0000
glycerate	**Carbohydrate**	**Glycolysis, gluconeogenesis, pyruvate metabolism**	1.21	0.0559	0.2073	-1.02	0.8820	0.6248	1.23	0.0689	1.0000
lactate	**Carbohydrate**	**Glycolysis, gluconeogenesis, pyruvate metabolism**	1.17	0.0371	0.1058	1.13	0.1242	0.3221	1.04	0.5845	1.0000
pyruvate	**Carbohydrate**	**Glycolysis, gluconeogenesis, pyruvate metabolism**	1.07	0.8272	0.6770	1.50	0.1939	0.3546	-1.41	0.0754	1.0000
arabinose	**Carbohydrate**	**Nucleotide sugars, pentose metabolism**	1.06	0.4027	0.5050	1.06	0.4461	0.4773	-1.00	0.9993	1.0000
arabitol	**Carbohydrate**	**Nucleotide sugars, pentose metabolism**	-1.15	0.1599	0.3430	-1.08	0.4329	0.4731	-1.06	0.5051	1.0000
gluconate	**Carbohydrate**	**Nucleotide sugars, pentose metabolism**	-1.65	0.1775	0.3554	-1.59	0.1900	0.3533	-1.04	0.8771	1.0000
ribitol	**Carbohydrate**	**Nucleotide sugars, pentose metabolism**	-1.05	0.6229	0.6121	1.05	0.5218	0.4984	-1.10	0.3305	1.0000
threitol	**Carbohydrate**	**Nucleotide sugars, pentose metabolism**	1.04	0.7438	0.6534	1.13	0.2537	0.3906	-1.09	0.5181	1.0000
xylitol	**Carbohydrate**	**Nucleotide sugars, pentose metabolism**	1.18	0.5601	0.5866	1.14	0.5962	0.5295	1.04	0.8983	1.0000
xylonate	**Carbohydrate**	**Nucleotide sugars, pentose metabolism**	-1.13	0.3833	0.4927	-1.26	0.1132	0.3143	1.12	0.3211	1.0000
xylose	**Carbohydrate**	**Nucleotide sugars, pentose metabolism**	1.70	0.0002	0.0028	1.30	0.1396	0.3314	1.31	0.1110	1.0000
arabonate	**Cofactors and vitamins**	**Ascorbate and aldarate metabolism**	-1.20	0.0740	0.2434	-1.13	0.2447	0.3847	-1.07	0.5830	1.0000
threonate	**Cofactors and vitamins**	**Ascorbate and aldarate metabolism**	1.30	0.0686	0.2335	1.21	0.1504	0.3371	1.07	0.4614	1.0000
pantothenate	**Cofactors and vitamins**	**Pantothenate and CoA metabolism**	1.31	0.2245	0.3816	1.29	0.1849	0.3515	1.02	0.9039	1.0000
citrate	**Energy**	**Krebs cycle**	-1.00	0.9837	0.7137	-1.06	0.5367	0.5033	1.06	0.5456	1.0000
malate	**Energy**	**Krebs cycle**	4.06	0.0002	0.0031	3.20	0.0001	0.0013	1.27	0.4818	1.0000
succinate	**Energy**	**Krebs cycle**	2.15	<0.0001	0.0000	1.74	<0.0001	0.0011	1.24	0.0246	1.0000
succinylcarnitine	**Energy**	**Krebs cycle**	-1.08	0.4996	0.5587	-1.04	0.7151	0.5745	-1.04	0.5566	1.0000
3-dehydrocarnitine*	**Lipid**	**Carnitine metabolism**	1.38	0.0271	0.1016	1.25	0.1012	0.3044	1.10	0.3495	1.0000
acetylcarnitine	**Lipid**	**Carnitine metabolism**	1.09	0.7158	0.6446	1.48	0.0230	0.1655	-1.35	0.1221	1.0000
carnitine	**Lipid**	**Carnitine metabolism**	1.05	0.4862	0.5519	1.02	0.7665	0.5914	1.03	0.6655	1.0000
propionylcarnitine	**Lipid**	**Fatty acid metabolism (also BCAA metabolism)**	1.60	0.0040	0.0309	1.24	0.1938	0.3546	1.29	0.1140	1.0000
3-hydroxypropanoate	**Lipid**	**Fatty acid, monohydroxy**	1.32	0.1908	0.3637	1.07	0.7478	0.5854	1.23	0.2292	1.0000
choline	**Lipid**	**Glycerolipid metabolism**	1.17	0.2235	0.3811	1.08	0.4745	0.4858	1.08	0.4428	1.0000
glycerol	**Lipid**	**Glycerolipid metabolism**	-1.02	0.8308	0.6779	-1.02	0.8654	0.6203	-1.00	0.9749	1.0000
glycerol 3-phosphate (G3P)	**Lipid**	**Glycerolipid metabolism**	1.38	0.1880	0.3620	1.64	0.0168	0.1410	-1.19	0.3375	1.0000
myo-inositol	**Lipid**	**Inositol metabolism**	1.46	0.0118	0.0702	1.13	0.4231	0.4698	1.29	0.0491	1.0000
1,2-propanediol	**Lipid**	**Ketone bodies**	4.14	0.0004	0.0046	3.25	0.0017	0.0236	1.27	0.3147	1.0000
3-hydroxybutyrate (BHBA)	**Lipid**	**Ketone bodies**	2.22	0.0120	0.0708	1.70	0.0686	0.2669	1.31	0.1935	1.0000
acetoacetate	**Lipid**	**Ketone bodies**	1.15	0.1576	0.3412	1.11	0.2639	0.3971	1.04	0.6262	1.0000
arachidonate (20:4n6)	**Lipid**	**Long chain fatty acid**	1.60	0.0025	0.0210	1.39	0.0241	0.1691	1.15	0.3053	1.0000
caproate (6:0)	**Lipid**	**Medium chain fatty acid**	1.51	0.0290	0.1035	1.15	0.0953	0.2989	1.31	0.1545	1.0000
caprylate (8:0)	**Lipid**	**Medium chain fatty acid**	1.44	0.1915	0.3641	1.04	0.7722	0.5932	1.39	0.2545	1.0000
1-stearoylglycerol (1-monostearin)	**Lipid**	**Monoacylglycerol**	2.05	0.0939	0.2749	-1.20	0.6711	0.5589	2.47	0.0346	1.0000
alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoc	**Lipid**	**Sterol/Steroid**	1.12	0.3724	0.4855	1.08	0.4592	0.4813	1.04	0.7744	1.0000
hypoxanthine	**Nucleotide**	**Purine metabolism, (hypo)xanthine/inosine containing**	1.14	0.2809	0.4158	1.17	0.2325	0.3761	-1.02	0.8617	1.0000
inosine	**Nucleotide**	**Purine metabolism, (hypo)xanthine/inosine containing**	1.07	0.4916	0.5547	1.11	0.2109	0.3598	-1.04	0.6732	1.0000
xanthine	**Nucleotide**	**Purine metabolism, (hypo)xanthine/inosine containing**	1.21	0.0945	0.2757	1.01	0.9390	0.6394	1.20	0.1413	1.0000
adenine	**Nucleotide**	**Purine metabolism, adenine containing**	1.10	0.6353	0.6168	1.28	0.1718	0.3466	-1.16	0.4814	1.0000
N6-carbamoylthreonyladenosine	**Nucleotide**	**Purine metabolism, guanine containing**	-1.07	0.6034	0.6046	1.01	0.9012	0.6298	-1.08	0.5326	1.0000
urate	**Nucleotide**	**Purine metabolism, urate metabolism**	1.08	0.4463	0.5307	1.08	0.4347	0.4736	1.00	0.9753	1.0000
cytidine	**Nucleotide**	**Pyrimidine metabolism, cytidine containing**	-1.23	0.1406	0.3271	-1.10	0.4084	0.4647	-1.12	0.3978	1.0000
pseudouridine	**Nucleotide**	**Pyrimidine metabolism, uracil containing**	1.01	0.9446	0.7053	1.02	0.8488	0.6158	-1.01	0.8899	1.0000
uridine	**Nucleotide**	**Pyrimidine metabolism, uracil containing**	1.03	0.6178	0.6102	-1.02	0.7829	0.5965	1.05	0.4343	1.0000
cyclo(leu-pro)	**Peptide**	**Dipeptide**	1.05	0.8355	0.6792	1.00	0.9916	0.6518	1.05	0.7973	1.0000
homocarnosine	**Peptide**	**Dipeptide derivative**	2.64	<0.0001	0.0001	2.77	<0.0001	0.0000	-1.05	0.7039	1.0000

Supplemental Digital Content 10

Supplemental Digital Content 10 (Figure). Metabolite pathways enriched in HIV subjects on ART. Quantitative Enrichment Analysis (QEA) was performed using metabolite set enrichment analysis (MSEA). QEA is based on the globaltest algorithm which uses a generalized linear model to estimate a Q-statistic for each metabolite set. CSF metabolites (n=107) from HIV-negative controls (n=14) and HIV subjects on ART with (n=12) and without (n=14) NCI and low plasma viral loads (VL<10,000 copies/ml) were inputted into MSEA and enrichment was assessed using the MSEA Metabolic Pathway library (n=88). Pathways were considered enriched when $p<0.05$ and FDR<5%.