Supplemental Methods: Bioinformatics and statistical analysis

Data processing

Metabolite data (raw counts from tandem mass spectrometry) was normalized by median centering. Missing values were imputed with the lower limit of detection for a given metabolite. Data normalization was used to reduce systematic bias in the data that may have arisen from instrumental or sampling problems, and to limit noise introduced by inter-subject heterogeneity.

Fold-change analysis

For between-group comparisons by fold-change analysis, significantly altered metabolites were defined by a fold change (FC) >1.2, p-value <0.05 and false discovery rate (FDR) ≤0.1. Multiple hypothesis testing corrections were performed by calculating the local false discovery rates using fdrtool in R.

Classification analysis

To identify metabolite clusters that distinguished between groups defined by HIV status or depression score cut-offs, classification analysis was performed by unsupervised hierarchical clustering in heatmaps, partial least squares discriminant analysis (PLS-DA), and Random Forest in the Metaboanalyst web portal (http://www.metaboanalyst.ca). Unsupervised and supervised classification analyses are methods used to reduce the complexity of high-dimensional datasets, assess differences between groups and/or phenotypes, and identify top-ranked features that best differentiate between groups. Unsupervised hierarchical clustering in heatmaps groups objects or subjects into "clusters" based on similarity, and begins with each sample as a separate cluster and then proceeds to combine all samples into one cluster. This process results in generation of a dendrogram and/or heatmap, which shows the hierarchy of the clusters. PLS-DA is a supervised method that uses multivariate regression techniques to perform classification and feature selection. The algorithm summarizes the original values into fewer variables using their weighted averages and uses cross-validation to select components for classification. Random Forest is a supervised learning algorithm that uses an ensemble of classification trees. Each tree is grown by random feature selection from a bootstrap sample of the dataset. Each branch is split using the best subset of predictors randomly chosen at that node. Classification is determined by the cumulative ensemble learning.

Correlation analysis

Pearson and Spearman correlation analysis were performed on log-transformed data in R. Pearson correlations were used to evaluate relationships between metabolites ($p<0.05$, $FDR \leq 0.1$). Spearman correlations were used to examine relationships between metabolites, depression scores, and K:T ratio. Correlation analyses were visualized using a correlation matrix constructed in R using the heatmap.2 function. Supervised hierarchical clustering was used to identify clusters of inter-related metabolites.

Pathway analysis

Metabolic pathways were extracted from the Kyoto Encyclopedia of Genes and Genomes (KEGG), Small Molecule Pathways Database (SMPDB), and PubChem. Biofunctions were extracted from Human Metabolome Database (HMDB) (www.hmdb.ca). Visualization of pathway mapping using metabolite information extracted from these databases was performed in Cytoscape.

Supplemental Table 1. Alterations in the plasma metabolome of HIV-positive and r
(current and nadir CD4 count). Subejcts with and without depression in the HIV-nega
metabolites were defined by a fold change (FC) >1.2 and p-value <0.01.

BIOCHEMICAL	SUPER_PATHWAY
alanine	Amino acid
beta-alanine	Amino acid
N-acetylalanine	Amino acid
2-aminobutyrate	Amino acid
creatine	Amino acid
creatinine	Amino acid
2-hydroxybutyrate (AHB)	Amino acid
cysteine	Amino acid
N-acetylmethionine	Amino acid
glutamine	Amino acid
pyroglutamine*	Amino acid
5-oxoproline	Amino acid
beta-hydroxypyruvate	Amino acid
betaine	Amino acid
dimethylglycine	Amino acid
glycine	Amino acid
N-acetylglycine	Amino acid
N-acetylserine	Amino acid
N-acetylthreonine	Amino acid
serine	Amino acid
threonine	Amino acid
4-acetamidobutanoate	Amino acid
3-methylhistidine	Amino acid
glutarylcarnitine (C5)	Amino acid
lysine	Amino acid
pipecolate	Amino acid
3-(4-hydroxyphenyl)lactate	Amino acid
3-methoxytyrosine	Amino acid
3-phenylpropionate (hydrocinnamate)	Amino acid
4-hydroxyphenylacetate	Amino acid
N-acetylphenylalanine	Amino acid
p-cresol sulfate	Amino acid
phenol sulfate	Amino acid
phenylacetate	Amino acid
phenylacetylglutamine	Amino acid
phenylalanine	Amino acid
phenyllactate (PLA)	Amino acid
tyrosine	Amino acid
3-indoxyl sulfate	Amino acid
C-glycosyltryptophan*	Amino acid
indoleacetate	Amino acid
indolelactate	Amino acid
indolepropionate	Amino acid
kynurenate	Amino acid
kynurenine	Amino acid

serotonin (5HT)	Amino acid
tryptophan	Amino acid
tryptophan betaine	Amino acid
arginine	Amino acid
citrulline	Amino acid
ornithine	Amino acid
proline	Amino acid
trans-4-hydroxyproline	Amino acid
urea	Amino acid
2-hydroxy-3-methylvalerate	Amino acid
2-methylbutyrylcarnitine (C5)	Amino acid
3-hydroxyisobutyrate	Amino acid
3-methyl-2-oxobutyrate	Amino acid
3-methyl-2-oxovalerate	Amino acid
3-methylglutarylcarnitine (C6)	Amino acid
4-methyl-2-oxopentanoate	Amino acid
alpha-hydroxyisovalerate	Amino acid
beta-hydroxyisovalerate	Amino acid
isobutyrylcarnitine	Amino acid
isoleucine	Amino acid
isovalerylcarnitine	Amino acid
leucine	Amino acid
valine	Amino acid
threonate	Cofactors and vitamins
bilirubin (E,E)*	Cofactors and vitamins
bilirubin (Z,Z)	Cofactors and vitamins
biliverdin	Cofactors and vitamins
heme	Cofactors and vitamins
urobilinogen	Cofactors and vitamins
nicotinamide	Cofactors and vitamins
pantothenate	Cofactors and vitamins
pyridoxate	Cofactors and vitamins
alpha-tocopherol	Cofactors and vitamins
gamma-CEHC	Cofactors and vitamins
gamma-tocopherol	Cofactors and vitamins
alpha-ketoglutarate	Energy
citrate	Energy
fumarate	Energy
malate	Energy
succinate	Energy
phosphate	Energy
cholate	Lipid
deoxycholate	Lipid
glycochenodeoxycholate	Lipid
glycocholate	Lipid
glycocholenate sulfate*	Lipid
glycodeoxycholate	Lipid
glycolithocholate sulfate*	Lipid
taurocholate	Lipid
taurocholenate sulfate*	Lipid
taurodeoxycholate	Lipid
3-dehydrocarnitine*	Lipid

acetylcarnitine	Lipid
carnitine	Lipid
cis-4-decenoyl carnitine	Lipid
decanoylcarnitine	Lipid
deoxycarnitine	Lipid
hexanoylcarnitine	Lipid
laurylcarnitine	Lipid
octanoylcarnitine	Lipid
oleoylcarnitine	Lipid
stearoylcarnitine	Lipid
docosahexaenoate (DHA; 22:6n3)	Lipid
docosapentaenoate (n3 DPA; 22:5n3)	Lipid
docosapentaenoate (n6 DPA; 22:5n6)	Lipid
eicosapentaenoate (EPA; 20:5n3)	Lipid
linoleate (18:2n6)	Lipid
linolenate [alpha or gamma; (18:3n3 or 6)]	Lipid
isovalerate	Lipid
butyrylcarnitine	Lipid
propionylcarnitine	Lipid
stearamide	Lipid
1,11-undecanedicarboxylate	Lipid
3-carboxy-4-methyl-5-propyl-2-furanpropanoate (CMPF)	Lipid
hexadecanedioate	Lipid
octadecanedioate	Lipid
sebacate (decanedioate)	Lipid
tetradecanedioate	Lipid
2-hydroxyoctanoate	Lipid
2-hydroxypalmitate	Lipid
2-hydroxystearate	Lipid
choline	Lipid
glycerol 3-phosphate (G3P)	Lipid
chiro-inositol	Lipid
3-hydroxybutyrate (BHBA)	Lipid
10-heptadecenoate (17:1n7)	Lipid
10-nonadecenoate (19:1n9)	Lipid
adrenate (22:4n6)	Lipid
arachidonate (20:4n6)	Lipid
cis-vaccenate (18:1n7)	Lipid
dihomo-linoleate (20:2n6)	Lipid
docosadienoate (22:2n6)	Lipid
eicosenoate (20:1n9 or 11)	Lipid
margarate (17:0)	Lipid
myristate (14:0)	Lipid
myristoleate (14:1n5)	Lipid
nonadecanoate (19:0)	Lipid
oleate (18:1n9)	Lipid
palmitate (16:0)	Lipid
palmitoleate (16:1n7)	Lipid
pentadecanoate (15:0)	Lipid
stearate (18:0)	Lipid
stearidonate (18:4n3)	Lipid
1-arachidonoylglycerophosphocholine*	Lipid

1-arachidonoylglycerophosphoethanolamine*	Lipid
1-arachidonoylglycerophosphoinositol*	Lipid
1-docosahexaenoylglycerophosphocholine*	Lipid
1-docosapentaenoylglycerophosphocholine*	Lipid
1-eicosadienoylglycerophosphocholine*	Lipid
1-eicosatrienoylglycerophosphocholine*	Lipid
1-linoleoylglycerophosphocholine	Lipid
1-linoleoylglycerophosphoethanolamine*	Lipid
1-myristoylglycerophosphocholine	Lipid
1-oleoylglycerophosphocholine	Lipid
1-oleoylglycerophosphoethanolamine	Lipid
1-palmitoleoylglycerophosphocholine*	Lipid
1-palmitoylglycerophosphocholine	Lipid
1-palmitoylglycerophosphoethanolamine	Lipid
1-palmitoylplasmenylethanolamine*	Lipid
1-pentadecanoylglycerophosphocholine*	Lipid
1-stearoylglycerophosphocholine	Lipid
1-stearoylglycerophosphoethanolamine	Lipid
2-arachidonoylglycerophosphocholine*	Lipid
2-arachidonoylglycerophosphoethanolamine*	Lipid
2-linoleoylglycerophosphocholine*	Lipid
2-linoleoylglycerophosphoethanolamine*	Lipid
2-myristoylglycerophosphocholine*	Lipid
2-oleoylglycerophosphocholine*	Lipid
2-oleoylglycerophosphoethanolamine*	Lipid
2-palmitoylglycerophosphocholine*	Lipid
2-palmitoylglycerophosphoethanolamine*	Lipid
10-undecenoate (11:1n1)	Lipid
caprate (10:0)	Lipid
caproate (6:0)	Lipid
caprylate (8:0)	Lipid
heptanoate (7:0)	Lipid
laurate (12:0)	Lipid
pelargonate (9:0)	Lipid
undecanoate (11:0)	Lipid
palmitoyl sphingomyelin	Lipid
sphinganine	Lipid
sphingosine	Lipid
stearoyl sphingomyelin	Lipid
21-hydroxypregnenolone disulfate	Lipid
4-androsten-3beta,17beta-diol disulfate 1*	Lipid
4-androsten-3beta,17beta-diol disulfate 2*	Lipid
5alpha-androstan-3alpha,17beta-diol disulfate	Lipid
5alpha-androstan-3beta,17beta-diol disulfate	Lipid
5alpha-pregnan-3beta,20alpha-diol disulfate	Lipid
7-alpha-hydroxy-3-oxo-4-cholestenoate (7-Hoca)	Lipid
andro steroid monosulfate 2*	Lipid
androsterone sulfate	Lipid
campesterol	Lipid
cholesterol	Lipid
cortisol	Lipid
cortisone	Lipid

dehydroisoandrosterone sulfate (DHEA-S)	Lipid
epiandrosterone sulfate	Lipid
lathosterol	Lipid
pregn steroid monosulfate*	Lipid
pregnen-diol disulfate*	Lipid
pregnenolone sulfate	Lipid
hypoxanthine	Nucleotide
adenosine 5'-monophosphate (AMP)	Nucleotide
N1-methyladenosine	Nucleotide
N6-carbamoylthreonyladenosine	Nucleotide
allantoin	Nucleotide
urate	Nucleotide
5-methyluridine (ribothymidine)	Nucleotide
pseudouridine	Nucleotide
uridine	Nucleotide
cyclo(leu-pro)	Peptide
tryptophylglutamate	Peptide
ADSGEGDFXAEGGGVR*	Peptide
DSGEGDFXAEGGGVR*	Peptide
gamma-glutamylisoleucine*	Peptide
gamma-glutamylleucine	Peptide
gamma-glutamylphenylalanine	Peptide
gamma-glutamyltyrosine	Peptide
bradykinin	Peptide
bradykinin, hydroxy-pro(3)	Peptide
HWESASLLR	Peptide
HWESASXX*	Peptide
XHWESASXXR*	Peptide

negative subjects with and without depression. Subjects with and without depression in the HIV-positive a
ative cohort were matched by age, gender, race, HCV status, smoking, drug use. Shown are metabolites

	HIV-positive test cohort		
SUB_PATHWAY	**Fold change**	**p-value**	**q-value**
Alanine and aspartate metabolism	-1.24	0.2183	0.4046
Alanine and aspartate metabolism	1.02	0.9414	0.7356
Alanine and aspartate metabolism	-1.09	0.3328	0.4959
Butanoate metabolism	-1.07	0.4690	0.5809
Creatine metabolism	-1.13	0.5176	0.6047
Creatine metabolism	-1.07	0.4734	0.5832
Cysteine, methionine, SAM, taurine metabolism	1.02	0.8949	0.7256
Cysteine, methionine, SAM, taurine metabolism	1.21	0.3314	0.4948
Cysteine, methionine, SAM, taurine metabolism	-1.35	0.1167	0.3378
Glutamate metabolism	-1.27	0.5766	0.6302
Glutamate metabolism	-1.07	0.7377	0.6856
Glutathione metabolism	-1.42	0.0544	0.2664
Glycine, serine and threonine metabolism	1.04	0.8683	0.7196
Glycine, serine and threonine metabolism	1.02	0.7951	0.7015
Glycine, serine and threonine metabolism	-1.28	0.1633	0.3705
Glycine, serine and threonine metabolism	-1.42	0.0077	0.1735
Glycine, serine and threonine metabolism	-1.02	0.9161	0.7303
Glycine, serine and threonine metabolism	-1.01	0.9725	0.7419
Glycine, serine and threonine metabolism	-1.22	0.2004	0.3908
Glycine, serine and threonine metabolism	-1.19	0.1753	0.3768
Glycine, serine and threonine metabolism	1.04	0.7217	0.6808
Guanidino and acetamido metabolism	1.47	0.0294	0.2444
Histidine metabolism	-1.61	0.1521	0.3640
Lysine metabolism	-1.18	0.2746	0.4480
Lysine metabolism	1.04	0.6893	0.6707
Lysine metabolism	1.04	0.8343	0.7115
Phenylalanine & tyrosine metabolism	-1.40	0.0834	0.3006
Phenylalanine & tyrosine metabolism	-1.13	0.2848	0.4570
Phenylalanine & tyrosine metabolism	-1.65	0.0650	0.2765
Phenylalanine & tyrosine metabolism	-2.68	0.0003	0.0257
Phenylalanine & tyrosine metabolism	-1.26	0.0397	0.2563
Phenylalanine & tyrosine metabolism	-1.95	0.0231	0.2351
Phenylalanine & tyrosine metabolism	1.18	0.4978	0.5953
Phenylalanine & tyrosine metabolism	-2.58	0.0002	0.0257
Phenylalanine & tyrosine metabolism	-1.85	0.0283	0.2431
Phenylalanine & tyrosine metabolism	-1.18	0.1197	0.3404
Phenylalanine & tyrosine metabolism	-1.31	0.1583	0.3677
Phenylalanine & tyrosine metabolism	-1.13	0.3197	0.4858
Tryptophan metabolism	-1.54	0.0745	0.2873
Tryptophan metabolism	-1.11	0.5106	0.6014
Tryptophan metabolism	-1.23	0.4601	0.5762
Tryptophan metabolism	-1.33	0.0258	0.2396
Tryptophan metabolism	1.15	0.6082	0.6425
Tryptophan metabolism	-1.07	0.7624	0.6926
Tryptophan metabolism	-1.12	0.3859	0.5328

Tryptophan metabolism	1.48	0.3359	0.4982
Tryptophan metabolism	-1.11	0.3646	0.5187
Tryptophan metabolism	-1.41	0.4690	0.5809
Urea cycle; arginine-, proline-, metabolism	-1.02	0.9409	0.7355
Urea cycle; arginine-, proline-, metabolism	-1.37	0.1068	0.3283
Urea cycle; arginine-, proline-, metabolism	-1.17	0.3592	0.5149
Urea cycle; arginine-, proline-, metabolism	-1.09	0.4049	0.5448
Urea cycle; arginine-, proline-, metabolism	-1.11	0.4121	0.5491
Urea cycle; arginine-, proline-, metabolism	-1.18	0.2387	0.4192
Valine, leucine and isoleucine metabolism	1.25	0.3722	0.5238
Valine, leucine and isoleucine metabolism	-1.27	0.0842	0.3520
Valine, leucine and isoleucine metabolism	1.00	0.9845	0.7442
Valine, leucine and isoleucine metabolism	-1.09	0.5164	0.6041
Valine, leucine and isoleucine metabolism	-1.15	0.2651	0.4397
Valine, leucine and isoleucine metabolism	-1.09	0.7797	0.6974
Valine, leucine and isoleucine metabolism	-1.12	0.4566	0.5744
Valine, leucine and isoleucine metabolism	1.14	0.5440	0.6165
Valine, leucine and isoleucine metabolism	-1.27	0.2210	0.4066
Valine, leucine and isoleucine metabolism	-1.77	0.0088	0.1825
Valine, leucine and isoleucine metabolism	-1.14	0.1632	0.3705
Valine, leucine and isoleucine metabolism	-1.84	0.0008	0.0456
Valine, leucine and isoleucine metabolism	-1.15	0.1934	0.3851
Valine, leucine and isoleucine metabolism	-1.03	0.6751	0.6661
Ascorbate and aldarate metabolism	1.30	0.1821	0.3801
Hemoglobin and porphyrin metabolism	1.09	0.8608	0.7178
Hemoglobin and porphyrin metabolism	1.17	0.7752	0.6961
Hemoglobin and porphyrin metabolism	-1.18	0.5934	0.6369
Hemoglobin and porphyrin metabolism	1.20	0.6712	0.6648
Hemoglobin and porphyrin metabolism	-1.67	0.1719	0.3751
Nicotinate and nicotinamide metabolism	-1.15	0.4478	0.5696
Pantothenate and CoA metabolism	1.40	0.0175	0.2225
Pyridoxal metabolism	1.33	0.2689	0.4428
Tocopherol metabolism	-1.22	0.3919	0.5367
Tocopherol metabolism	-1.16	0.4454	0.5683
Tocopherol metabolism	-1.48	0.1256	0.3454
Krebs cycle	1.64	0.0641	0.2758
Krebs cycle	2.30	0.1272	0.3466
Krebs cycle	1.15	0.2383	0.4189
Krebs cycle	1.13	0.5346	0.6124
Krebs cycle	1.24	0.2018	0.3920
Oxidative phosphorylation	-1.11	0.0334	0.2496
Bile acid metabolism	-1.18	0.5087	0.6005
Bile acid metabolism	-1.66	0.1182	0.3391
Bile acid metabolism	-1.34	0.2786	0.4516
Bile acid metabolism	-1.38	0.1636	0.3707
Bile acid metabolism	1.25	0.4290	0.5591
Bile acid metabolism	-1.97	0.0261	0.2400
Bile acid metabolism	1.07	0.8235	0.7088
Bile acid metabolism	1.60	0.1428	0.3581
Bile acid metabolism	2.09	0.0217	0.2325
Bile acid metabolism	1.31	0.5693	0.6272
Carnitine metabolism	-1.39	0.0465	0.2616

Carnitine metabolism	-1.09	0.5734	0.6289
Carnitine metabolism	-1.07	0.3823	0.5305
Carnitine metabolism	-1.50	0.1332	0.3513
Carnitine metabolism	-1.39	0.2381	0.4187
Carnitine metabolism	-1.26	0.0250	0.2383
Carnitine metabolism	-1.44	0.1598	0.3686
Carnitine metabolism	-1.63	0.0501	0.2640
Carnitine metabolism	-1.34	0.3273	0.4917
Carnitine metabolism	-1.31	0.1287	0.3478
Carnitine metabolism	-1.50	0.0529	0.2656
Essential fatty acid	1.27	0.3198	0.4859
Essential fatty acid	-1.04	0.8774	0.7217
Essential fatty acid	1.48	0.1856	0.3817
Essential fatty acid	1.02	0.9210	0.7313
Essential fatty acid	-1.06	0.7066	0.6762
Essential fatty acid	-1.05	0.8166	0.7070
Fatty acid metabolism	-1.71	0.0705	0.2809
Fatty acid metabolism (also BCAA metabolism)	-1.24	0.1935	0.3851
Fatty acid metabolism (also BCAA metabolism)	-1.40	0.0545	0.2664
Fatty acid, amide	1.01	0.9632	0.7400
Fatty acid, dicarboxylate	-1.06	0.7207	0.6805
Fatty acid, dicarboxylate	-1.45	0.2489	0.4259
Fatty acid, dicarboxylate	-1.13	0.5608	0.6237
Fatty acid, dicarboxylate	-1.39	0.1238	0.3439
Fatty acid, dicarboxylate	-1.52	0.0938	0.3140
Fatty acid, dicarboxylate	-1.36	0.0955	0.3160
Fatty acid, monohydroxy	-1.42	0.0301	0.2452
Fatty acid, monohydroxy	-1.16	0.4797	0.5864
Fatty acid, monohydroxy	-1.11	0.6261	0.6492
Glycerolipid metabolism	1.10	0.0606	0.2726
Glycerolipid metabolism	1.12	0.7294	0.6831
Inositol metabolism	-1.79	0.1679	0.3730
Ketone bodies	-1.29	0.2842	0.4565
Long chain fatty acid	1.14	0.4412	0.5660
Long chain fatty acid	1.08	0.6514	0.6581
Long chain fatty acid	1.03	0.8792	0.7221
Long chain fatty acid	1.20	0.4796	0.5863
Long chain fatty acid	-1.22	0.3664	0.5199
Long chain fatty acid	1.26	0.2459	0.4239
Long chain fatty acid	1.32	0.2101	0.3985
Long chain fatty acid	-1.03	0.8805	0.7224
Long chain fatty acid	-1.03	0.7969	0.7020
Long chain fatty acid	1.04	0.7442	0.6874
Long chain fatty acid	1.14	0.5452	0.6170
Long chain fatty acid	-1.02	0.8394	0.7127
Long chain fatty acid	1.17	0.4027	0.5434
Long chain fatty acid	-1.01	0.9606	0.7395
Long chain fatty acid	1.16	0.4315	0.5605
Long chain fatty acid	1.10	0.4238	0.5560
Long chain fatty acid	-1.03	0.7895	0.7000
Long chain fatty acid	1.13	0.6293	0.6503
Lysolipid	1.09	0.5963	0.6380

Lysolipid	-1.26	0.1028	0.3242
Lysolipid	-1.74	0.0017	0.0727
Lysolipid	-1.08	0.6758	0.6664
Lysolipid	1.02	0.9144	0.7299
Lysolipid	-1.22	0.3267	0.4912
Lysolipid	-1.10	0.5814	0.6321
Lysolipid	-1.39	0.0522	0.2652
Lysolipid	-1.72	0.0038	0.1237
Lysolipid	-1.21	0.4015	0.5427
Lysolipid	-1.27	0.1936	0.3852
Lysolipid	-1.12	0.3779	0.5276
Lysolipid	-1.22	0.2914	0.4627
Lysolipid	-1.06	0.7222	0.6810
Lysolipid	1.07	0.6069	0.6420
Lysolipid	1.20	0.5450	0.6170
Lysolipid	-1.06	0.6926	0.6718
Lysolipid	-1.49	0.1118	0.3332
Lysolipid	1.13	0.2627	0.4377
Lysolipid	-1.21	0.2090	0.3976
Lysolipid	-1.10	0.5705	0.6277
Lysolipid	-1.61	0.0173	0.2219
Lysolipid	-1.36	0.1720	0.3751
Lysolipid	-1.03	0.9138	0.7298
Lysolipid	-1.38	0.0834	0.3006
Lysolipid	-1.37	0.1026	0.3240
Lysolipid	-1.07	0.7575	0.6912
Lysolipid	1.36	0.1875	0.3825
Medium chain fatty acid	-1.01	0.9797	0.7433
Medium chain fatty acid	-1.11	0.3593	0.5150
Medium chain fatty acid	-1.75	0.0163	0.2189
Medium chain fatty acid	-1.33	0.1533	0.3648
Medium chain fatty acid	-1.65	0.0202	0.2293
Medium chain fatty acid	-1.07	0.4506	0.5711
Medium chain fatty acid	-1.16	0.4081	0.5467
Medium chain fatty acid	1.06	0.5438	0.6164
Sphingolipid	-1.21	0.0358	0.2524
Sphingolipid	1.87	0.0444	0.2601
Sphingolipid	1.91	0.0705	0.2809
Sphingolipid	-1.29	0.1003	0.3215
Sterol/Steroid	-1.31	0.0706	0.2809
Sterol/Steroid	-1.52	0.2164	0.4032
Sterol/Steroid	1.12	0.5582	0.6226
Sterol/Steroid	-1.04	0.8835	0.7231
Sterol/Steroid	-1.98	0.1132	0.3346
Sterol/Steroid	1.36	0.2568	0.4327
Sterol/Steroid	1.23	0.2367	0.4178
Sterol/Steroid	1.57	0.0658	0.2772
Sterol/Steroid	-1.75	0.1859	0.3818
Sterol/Steroid	-1.34	0.4067	0.5459
Sterol/Steroid	-1.09	0.1740	0.3762
Sterol/Steroid	-1.39	0.0427	0.2588
Sterol/Steroid	-1.21	0.1568	0.3668

Sterol/Steroid	-1.04	0.8750	0.7211
Sterol/Steroid	-1.58	0.3144	0.4816
Sterol/Steroid	1.08	0.7184	0.6798
Sterol/Steroid	1.01	0.9526	0.7379
Sterol/Steroid	-1.25	0.3943	0.5382
Sterol/Steroid	-1.19	0.3559	0.5126
Purine metabolism, (hypo)xanthine/inosine containing	1.87	0.0637	0.2754
Purine metabolism, adenine containing	-1.55	0.2460	0.4240
Purine metabolism, adenine containing	-1.06	0.7890	0.6999
Purine metabolism, guanine containing	-1.05	0.7935	0.7011
Purine metabolism, urate metabolism	-1.23	0.4387	0.5646
Purine metabolism, urate metabolism	-1.24	0.0186	0.2255
Pyrimidine metabolism, uracil containing	-1.11	0.4056	0.5452
Pyrimidine metabolism, uracil containing	1.09	0.4464	0.5688
Pyrimidine metabolism, uracil containing	1.23	0.0430	0.2591
Dipeptide	1.01	0.9882	0.7449
Dipeptide	1.10	0.7601	0.6920
Fibrinogen cleavage peptide	-1.29	0.6949	0.6725
Fibrinogen cleavage peptide	-1.24	0.6278	0.6498
gamma-glutamyl	-1.89	0.0062	0.1585
gamma-glutamyl	-1.63	0.0444	0.2601
gamma-glutamyl	-1.38	0.1454	0.3598
gamma-glutamyl	-1.49	0.0513	0.2647
Polypeptide	-1.45	0.5719	0.6283
Polypeptide	-1.16	0.7683	0.6942
Polypeptide	-1.80	0.3008	0.4706
Polypeptide	-2.03	0.1670	0.3725
Polypeptide	-1.06	0.9295	0.7331

nd test cohorts were matched by age, gender, HCV status, drug use, and stage of disease
detected across all three cohorts following data pre-processing. Significantly altered

HIV-positive validation cohort			HIV-negative cohort		
Fold change	**p-value**	**q-value**	**Fold change**	**p-value**	**q-value**
1.11	0.4093	0.7925	-1.01	0.8777	0.8198
-1.59	0.0256	0.4814	-1.73	0.1185	0.5934
-1.09	0.2232	0.6757	1.03	0.6371	0.7676
-1.21	0.2510	0.7008	-1.01	0.9836	0.8361
-1.23	0.2997	0.7367	-1.31	0.2172	0.6111
-1.03	0.7362	0.8730	-1.13	0.1349	0.5967
-1.11	0.5527	0.8376	-1.03	0.9134	0.8257
1.01	0.9141	0.8951	-1.13	0.3429	0.6564
-1.05	0.8522	0.8883	-1.15	0.3850	0.6663
1.01	0.9410	0.8978	-1.05	0.6337	0.7667
-1.30	0.3786	0.7794	1.31	0.3618	0.6611
-1.17	0.2250	0.6774	1.03	0.7798	0.8017
-1.13	0.4523	0.8085	-1.11	0.5949	0.7552
-1.04	0.5765	0.8433	1.18	0.1418	0.5979
-1.38	0.1906	0.6465	-1.07	0.6750	0.7778
1.01	0.9704	0.9006	1.03	0.8651	0.8177
1.16	0.6369	0.8560	1.21	0.4776	0.7123
1.03	0.7199	0.8705	-1.12	0.3526	0.6589
-1.26	0.2029	0.6544	-1.34	0.1422	0.5980
-1.01	0.9078	0.8944	-1.13	0.2694	0.6329
-1.06	0.5991	0.8483	-1.13	0.3253	0.6516
1.03	0.7197	0.8704	-1.15	0.1447	0.5984
-1.57	0.2682	0.7145	-1.50	0.3582	0.6602
-1.06	0.5950	0.8474	1.08	0.5111	0.7260
-1.02	0.8074	0.8828	-1.13	0.1907	0.6040
1.13	0.6199	0.8526	-1.17	0.5090	0.7252
1.13	0.2866	0.7279	1.10	0.4321	0.6914
1.22	0.1589	0.6397	1.16	0.1952	0.6044
-1.20	0.3507	0.7660	-1.39	0.1590	0.6005
-1.53	0.0863	0.6074	1.13	0.7228	0.7894
-1.39	0.1219	0.6277	-1.20	0.3903	0.6693
1.22	0.6239	0.8534	1.00	0.9899	0.8369
1.16	0.5443	0.8355	-1.10	0.7010	0.7842
-1.04	0.8539	0.8885	-2.17	0.0007	0.0672
-1.28	0.3184	0.7482	1.07	0.7497	0.7954
-1.08	0.2631	0.7106	-1.16	0.1144	0.5924
1.16	0.4016	0.7894	1.40	0.0623	0.5695
-1.05	0.5885	0.8460	-1.18	0.0982	0.5877
-1.19	0.4071	0.7917	-1.13	0.5437	0.7382
1.04	0.5828	0.8447	1.09	0.3932	0.6709
-1.45	0.2572	0.7059	-1.21	0.5326	0.7341
1.02	0.8950	0.8931	1.03	0.8734	0.8191
-1.12	0.6610	0.8605	-1.19	0.4554	0.7025
1.09	0.5306	0.8320	-1.07	0.6541	0.7723
1.05	0.6224	0.8531	1.05	0.7927	0.8043

-1.49	0.2258	0.6782	-1.34	0.1907	0.6040
-1.16	0.0861	0.6073	-1.05	0.6304	0.7657
-1.76	0.1761	0.6437	-1.61	0.2475	0.6237
-1.09	0.7114	0.8691	-1.75	0.0942	0.5863
-1.16	0.3327	0.7564	-1.35	0.0175	0.4677
-1.46	0.0226	0.4723	-1.35	0.0523	0.5604
-1.07	0.5899	0.8463	-1.10	0.4098	0.6800
-1.29	0.0717	0.5941	-1.46	0.0721	0.5761
-1.17	0.1546	0.6386	-1.11	0.3168	0.6491
1.04	0.8066	0.8827	1.43	0.0921	0.5855
-1.57	0.0046	0.2896	-1.44	0.0443	0.5505
-1.09	0.3645	0.7728	-1.09	0.6195	0.7626
1.04	0.5417	0.8349	1.02	0.8924	0.8223
-1.24	0.1182	0.6261	-1.13	0.3614	0.6610
-1.01	0.9814	0.9016	1.01	0.9821	0.8359
-1.20	0.1948	0.6472	-1.12	0.5090	0.7252
1.32	0.1840	0.6453	1.85	0.0210	0.4879
-1.01	0.9344	0.8971	1.04	0.7463	0.7946
-2.17	0.0011	0.1138	-2.21	0.0002	0.0384
-1.29	0.0436	0.5481	-1.15	0.1840	0.6034
-1.51	0.0192	0.4592	-1.68	0.0319	0.5268
-1.22	0.0912	0.6111	-1.11	0.3255	0.6517
-1.13	0.1718	0.6428	-1.13	0.1489	0.5990
-1.56	0.1047	0.6195	-1.69	0.1158	0.5927
-1.20	0.6393	0.8565	-1.04	0.9006	0.8236
1.24	0.6349	0.8556	-1.48	0.1569	0.6002
-1.06	0.8536	0.8885	-1.28	0.4319	0.6913
-1.01	0.9841	0.9018	1.21	0.3277	0.6523
1.60	0.3888	0.7840	1.71	0.2691	0.6328
-1.11	0.5909	0.8465	-1.04	0.8485	0.8148
-1.16	0.4680	0.8137	-1.54	0.0685	0.5739
-1.22	0.4841	0.8188	-1.59	0.1503	0.5993
-1.00	0.9649	0.9001	-1.20	0.0720	0.5760
1.35	0.2511	0.7009	-1.58	0.0888	0.5843
1.34	0.1969	0.6476	1.01	0.9761	0.8350
-1.05	0.8802	0.8915	-1.18	0.6263	0.7646
1.18	0.0435	0.5479	1.02	0.8587	0.8166
-1.07	0.5641	0.8404	1.06	0.6099	0.7597
1.12	0.2869	0.7281	-1.02	0.9266	0.8277
-1.02	0.9186	0.8955	-1.01	0.8806	0.8203
1.01	0.9066	0.8943	-1.10	0.1567	0.6002
1.41	0.2876	0.7286	-1.68	0.2870	0.6395
-1.03	0.8816	0.8916	-1.45	0.1257	0.5949
1.67	0.1822	0.6449	-1.99	0.1519	0.5995
1.39	0.4651	0.8128	-1.69	0.3106	0.6472
1.42	0.1688	0.6421	1.31	0.1618	0.6008
1.02	0.9508	0.8987	-2.76	0.0446	0.5509
-1.07	0.9086	0.8945	1.04	0.9135	0.8257
1.01	0.9793	0.9014	-2.62	0.0737	0.5770
1.32	0.1294	0.6306	-1.18	0.6426	0.7692
-1.16	0.7943	0.8811	-1.80	0.1937	0.6043
-1.04	0.7486	0.8748	-1.34	0.0748	0.5777

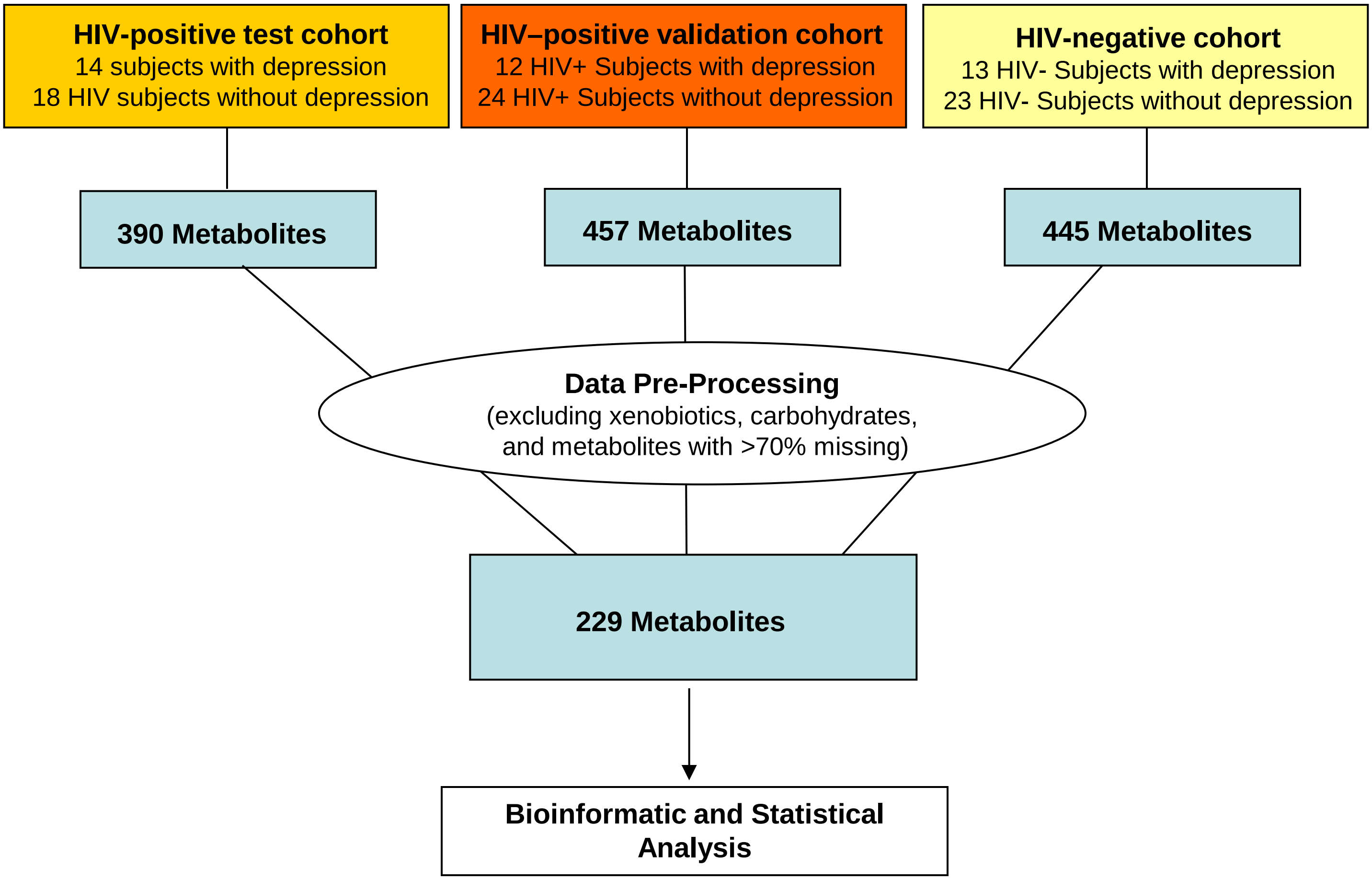
1.02	0.8972	0.8933	-1.02	0.8966	0.8230
-1.18	0.1516	0.6378	-1.15	0.1268	0.5952
1.02	0.9144	0.8951	1.10	0.6993	0.7838
-1.05	0.8418	0.8871	1.10	0.7802	0.8018
-1.07	0.5649	0.8406	1.20	0.0813	0.5810
-1.05	0.8008	0.8820	-1.16	0.6061	0.7586
1.06	0.7946	0.8812	1.59	0.1532	0.5997
-1.05	0.8338	0.8861	1.12	0.6783	0.7786
-1.01	0.9502	0.8987	1.10	0.7022	0.7845
-1.05	0.7904	0.8806	-1.03	0.8752	0.8194
1.07	0.5983	0.8481	1.38	0.2126	0.6098
1.04	0.8547	0.8886	1.16	0.6216	0.7632
-1.02	0.8530	0.8884	1.33	0.1829	0.6032
1.11	0.5123	0.8270	1.23	0.3140	0.6483
1.15	0.4590	0.8108	-1.05	0.8745	0.8193
1.30	0.2685	0.7148	-1.03	0.9385	0.8295
1.09	0.6417	0.8569	-1.27	0.1987	0.6055
-1.20	0.2487	0.6989	-1.34	0.0720	0.5760
-1.66	0.0001	0.0207	-1.48	0.0149	0.4483
-1.07	0.6223	0.8531	1.09	0.4722	0.7100
-1.10	0.6946	0.8664	-1.13	0.3852	0.6664
-1.00	0.9916	0.9025	1.22	0.6583	0.7734
1.20	0.4586	0.8106	1.20	0.5071	0.7245
1.49	0.1408	0.6346	1.60	0.1488	0.5990
1.57	0.3991	0.7884	-1.54	0.0301	0.5220
1.33	0.1436	0.6354	-1.13	0.4610	0.7050
1.25	0.2790	0.7225	-1.12	0.4620	0.7055
1.03	0.6852	0.8648	1.12	0.4403	0.6954
-1.09	0.3125	0.7447	1.16	0.2980	0.6432
1.02	0.8291	0.8856	1.00	0.9753	0.8349
1.16	0.3175	0.7477	1.00	0.9754	0.8349
1.15	0.7899	0.8806	-2.42	0.1410	0.5978
1.28	0.6095	0.8505	-1.01	0.9761	0.8350
1.13	0.6360	0.8558	1.17	0.6850	0.7803
1.06	0.8479	0.8878	1.08	0.8733	0.8191
1.04	0.8430	0.8872	-1.08	0.7429	0.7939
-1.18	0.1752	0.6435	1.19	0.2472	0.6236
1.27	0.1940	0.6471	1.06	0.8229	0.8101
1.12	0.6533	0.8591	1.21	0.6164	0.7617
1.08	0.7314	0.8722	1.21	0.5766	0.7493
1.17	0.5753	0.8430	1.06	0.8835	0.8208
-1.07	0.7199	0.8705	1.01	0.9702	0.8342
1.25	0.2862	0.7276	1.23	0.3782	0.6648
1.62	0.1178	0.6259	1.61	0.2397	0.6201
-1.07	0.5861	0.8454	-1.09	0.6379	0.7678
1.21	0.4156	0.7950	-1.10	0.7503	0.7955
1.23	0.1952	0.6473	1.01	0.9755	0.8349
1.51	0.1839	0.6453	1.45	0.3806	0.6654
1.02	0.8359	0.8864	-1.05	0.7784	0.8014
1.04	0.7879	0.8803	1.04	0.8321	0.8118
1.37	0.1558	0.6389	1.29	0.4260	0.6884
-1.06	0.6704	0.8622	-1.05	0.5923	0.7544

-1.59	0.0456	0.5529	1.18	0.5647	0.7454
1.36	0.0297	0.5018	-1.13	0.3867	0.6672
1.07	0.7236	0.8710	1.15	0.3105	0.6472
1.08	0.5504	0.8371	-1.07	0.4945	0.7194
-1.29	0.1515	0.6377	-1.18	0.4457	0.6980
-1.13	0.4806	0.8177	-1.12	0.4602	0.7047
-1.14	0.4088	0.7923	-1.22	0.2331	0.6169
-1.48	0.1050	0.6196	1.01	0.9690	0.8340
1.04	0.8697	0.8903	-1.15	0.5158	0.7278
-1.11	0.5568	0.8386	-1.21	0.2264	0.6136
-1.31	0.1948	0.6472	-1.20	0.3703	0.6631
-1.02	0.9298	0.8967	-1.13	0.4790	0.7129
-1.09	0.4273	0.7995	-1.14	0.2212	0.6122
-1.08	0.6246	0.8536	1.19	0.1702	0.6019
-1.30	0.1242	0.6286	-1.07	0.5935	0.7547
-1.40	0.0505	0.5633	-1.18	0.1894	0.6039
-1.14	0.4824	0.8183	-1.32	0.2185	0.6115
-1.13	0.4050	0.7908	-1.20	0.1102	0.5913
-1.02	0.8804	0.8915	-1.16	0.1861	0.6036
-1.54	0.0256	0.4814	1.01	0.9579	0.8324
-1.13	0.5288	0.8315	-1.43	0.0697	0.5746
-1.33	0.1256	0.6292	-1.06	0.8059	0.8069
1.18	0.3251	0.7521	-1.04	0.8412	0.8135
-1.11	0.5287	0.8315	-1.18	0.3226	0.6508
-1.26	0.1842	0.6453	-1.22	0.3080	0.6464
-1.10	0.5425	0.8351	-1.30	0.0980	0.5876
-1.19	0.4084	0.7922	1.34	0.1591	0.6005
-1.19	0.2462	0.6968	-1.04	0.8688	0.8183
1.45	0.0836	0.6053	1.12	0.4299	0.6903
1.06	0.4387	0.8037	1.00	0.9617	0.8330
1.56	0.0367	0.5285	-1.03	0.7950	0.8048
1.14	0.4964	0.8225	1.46	0.0042	0.2618
1.49	0.1310	0.6312	-1.03	0.8440	0.8140
1.27	0.1268	0.6296	1.04	0.5285	0.7326
1.12	0.0729	0.5953	-1.00	0.9457	0.8306
-1.02	0.8037	0.8824	1.03	0.7086	0.7861
-1.24	0.4734	0.8154	-1.32	0.3463	0.6573
-1.18	0.3511	0.7662	-1.14	0.5250	0.7313
1.04	0.7701	0.8779	1.11	0.5247	0.7312
1.59	0.0127	0.4195	1.11	0.6673	0.7758
1.14	0.7013	0.8675	1.27	0.5479	0.7396
1.39	0.1127	0.6236	1.24	0.2261	0.6135
1.02	0.9185	0.8955	-1.03	0.8890	0.8217
-1.24	0.4960	0.8224	1.09	0.8599	0.8168
1.22	0.3371	0.7588	1.33	0.4373	0.6939
1.18	0.3280	0.7538	1.43	0.0101	0.3957
1.29	0.4943	0.8219	1.07	0.8357	0.8125
-1.70	0.1384	0.6338	-1.66	0.2806	0.6372
-1.30	0.3284	0.7540	-1.34	0.2859	0.6391
1.02	0.7856	0.8800	-1.05	0.4994	0.7214
1.56	0.0471	0.5563	1.01	0.9764	0.8351
1.09	0.4707	0.8146	1.22	0.2188	0.6116

-1.03	0.9236	0.8961	-1.43	0.2796	0.6368
-1.96	0.1025	0.6182	-1.72	0.3242	0.6513
1.78	0.0235	0.4752	-1.57	0.1822	0.6032
1.36	0.1011	0.6174	-1.27	0.4882	0.7168
1.76	0.0234	0.4749	1.38	0.3336	0.6539
1.40	0.0602	0.5797	1.14	0.6811	0.7793
-1.01	0.9409	0.8978	-1.06	0.6334	0.7666
-1.13	0.7507	0.8751	-1.31	0.3672	0.6624
1.04	0.5542	0.8380	1.08	0.3652	0.6619
1.05	0.6423	0.8570	1.06	0.5268	0.7320
1.05	0.8690	0.8902	-1.64	0.1072	0.5905
1.04	0.6510	0.8587	-1.06	0.3349	0.6543
-1.18	0.2295	0.6817	-1.11	0.4695	0.7088
-1.00	0.9749	0.9010	1.10	0.1458	0.5986
1.02	0.8495	0.8880	1.08	0.3126	0.6479
-1.15	0.6304	0.8547	-1.22	0.5996	0.7566
-1.23	0.2912	0.7310	-1.08	0.7279	0.7905
-1.07	0.9112	0.8948	2.38	0.2270	0.6138
1.18	0.8037	0.8824	3.44	0.1430	0.5981
-1.28	0.1754	0.6435	-1.13	0.4564	0.7029
-1.38	0.0067	0.3416	-1.17	0.1910	0.6040
-1.16	0.0912	0.6111	-1.11	0.1708	0.6019
-1.06	0.5208	0.8294	-1.09	0.4831	0.7147
-1.73	0.5766	0.8433	-2.42	0.3849	0.6663
1.15	0.7109	0.8690	1.31	0.5866	0.7526
1.03	0.8776	0.8912	1.22	0.3434	0.6565
-1.64	0.0960	0.6143	1.02	0.9530	0.8317
-1.67	0.2012	0.6525	1.62	0.2691	0.6328

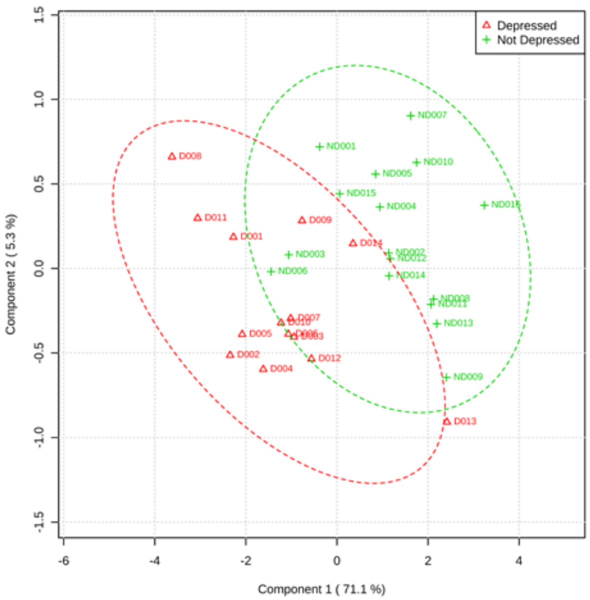
Supplemental Figure 1. Strategy used to identify plasma metabolites altered in subjects with compared to without depressive symptoms. Untargeted metabolomic profiling was performed on 104 plasma samples from three independent cohorts (HIV-positive test cohort, HIV-positive validation cohort, and HIV-negative cohort).

Supplementary Figure 1

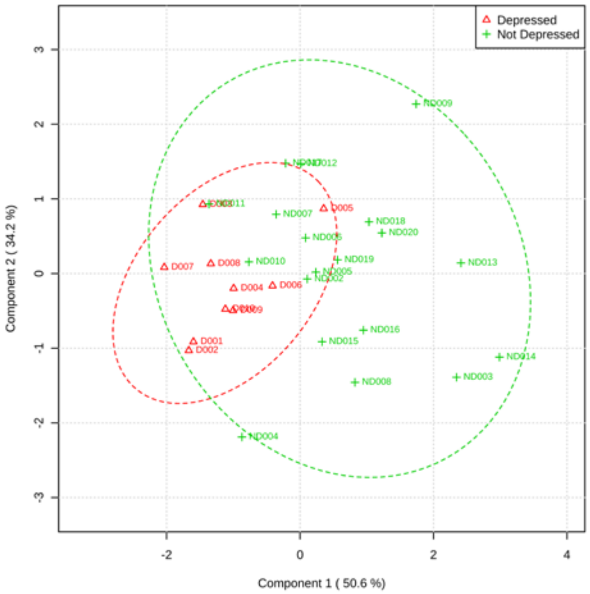


Supplemental Figure 2. PLS-DA analysis of signature metabolites shows separation of metabolomes of subjects with compared to without depressive symptoms. Shown are analyses from the HIV-positive test cohort (n=6 metabolites), HIV-positive validation cohort (n=5 metabolites), and HIV-negative test cohort (n=5 metabolites). P-values from the permutation test were used to assess class discrimination.

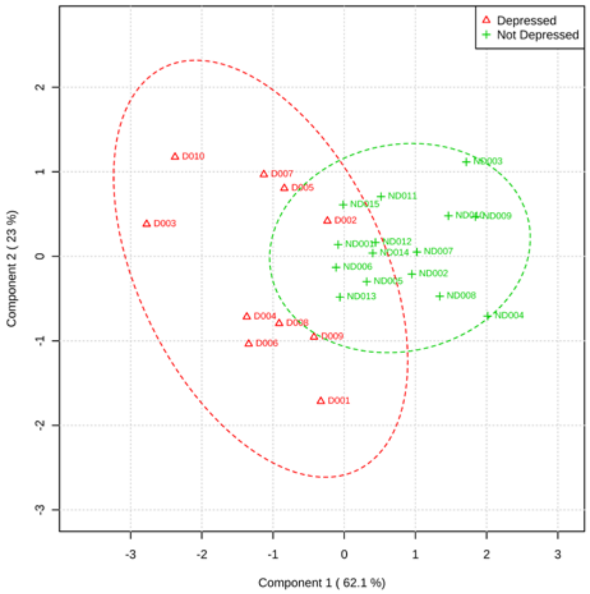
Supplementary Figure 2



HIV-positive test cohort



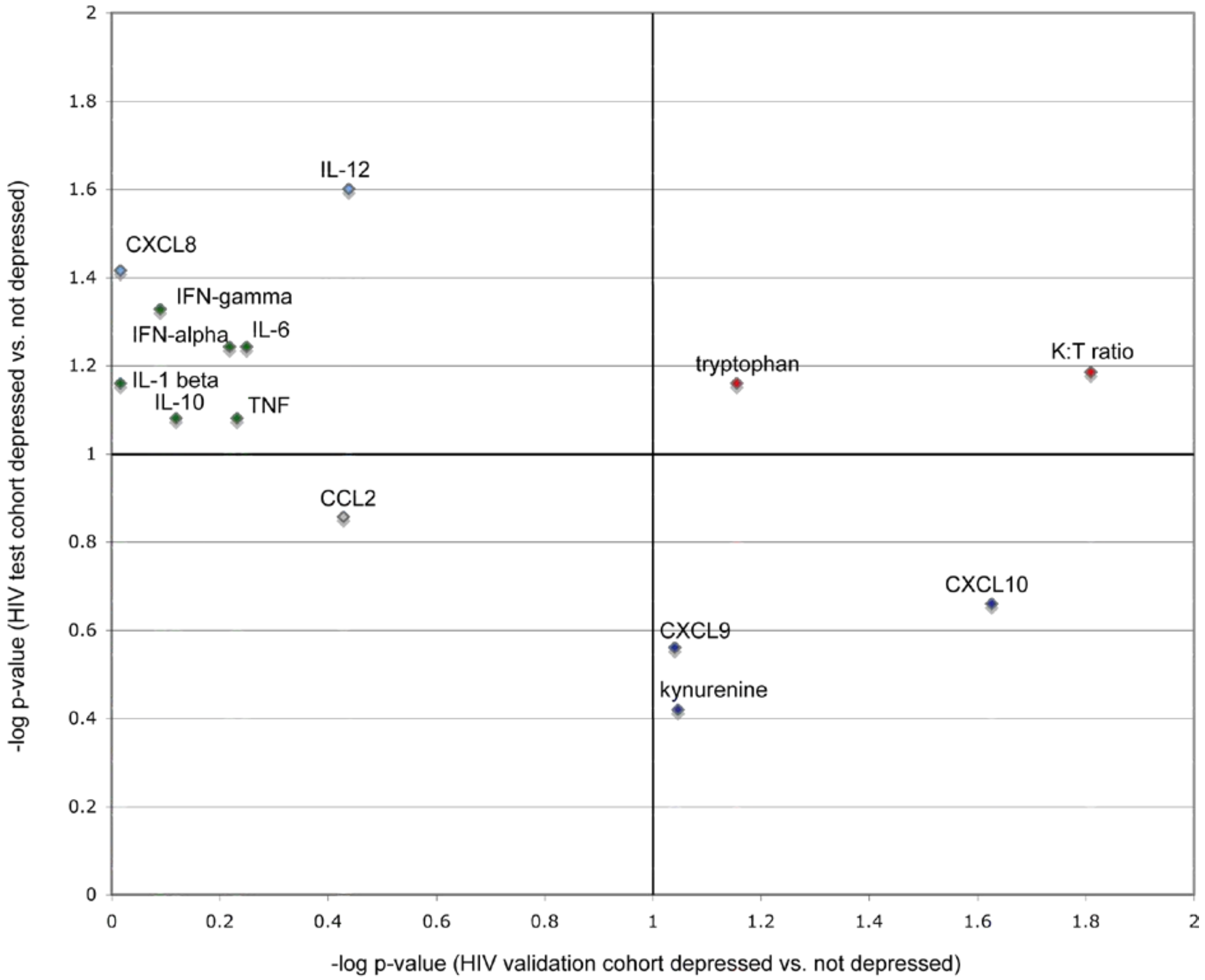
HIV-positive validation cohort



HIV-negative cohort

Supplemental Figure 3. P-value scatter plot of metabolites related to tryptophan catabolism (tryptophan, kynurenine, and K:T ratio) and inflammation markers altered in the HIV-infected individuals with vs. without depressive symptoms. The X- and Y-axis shows $–\log_{10}$ p-values of markers of tryptophan catabolism and inflammation in subjects with versus without depressive symptoms from the HIV-positive test and validation cohorts (n=22 and 18, respectively). The analyses were limited to subjects <50 years old to minimize confounding effects of age on inflammation markers and groups were matched for age, race, gender, and other clinical covariates as described in the Results.

Supplementary Figure 3



Supplemental Figure 4. Inter-relationships between plasma metabolites, depression scores, and markers of tryptophan catabolism in HIV-negative subjects. The correlation matrix and clinical covariate bar were constructed in R using the heatmap.2 function. Pearson correlations were used to evaluate relationships between metabolites ($p<0.05$, $FDR \leq 0.1$). Spearman correlations were used to examine relationships between metabolites, depression scores, and K:T ratio. Significant correlations had a $-0.32> r >0.32$, $p<0.05$, and FDR<10%. Red and blue indicate positive and negative correlations, respectively (see Color Key).

HIV-negative cohort