

### HIV+ NCs vs HIV- NCs: Pathway analysis

Pathway	Total	Hits	Raw p	$-\log_{10}(p)$	Holm adjus	FDR	Impact
Aminoacyl-tRNA biosynthesis	48	11	0.00014135	3.8497	0.011873	0.011873	0.1667
D-Glutamine and D-glutamate metabolism	6	3	0.0045202	2.3448	0.37518	0.18985	0.5
Arginine biosynthesis	14	4	0.0098832	2.0051	0.81043	0.27673	0.4213
Glyoxylate and dicarboxylate metabolism	32	6	0.014237	1.8466	1	0.29897	0.3968
Phenylalanine, tyrosine and tryptophan biosynthesis	4	2	0.022701	1.644	1	0.38138	1
Alanine, aspartate and glutamate metabolism	28	5	0.030262	1.5191	1	0.42367	0.4455
Nitrogen metabolism	6	2	0.052121	1.283	1	0.60359	0
Butanoate metabolism	15	3	0.06727	1.1722	1	0.60359	0.0318
Arachidonic acid metabolism	36	5	0.077336	1.1116	1	0.60359	0.3337
Glycerophospholipid metabolism	36	5	0.077336	1.1116	1	0.60359	0.3991
Histidine metabolism	16	3	0.079042	1.1021	1	0.60359	0.2213
Valine, leucine and isoleucine biosynthesis	8	2	0.089436	1.0485	1	0.62605	0
Pentose and glucuronate interconversions	18	3	0.10502	0.97871	1	0.67861	0.4219
Phenylalanine metabolism	10	2	0.13225	0.8786	1	0.79351	0.3571
Glycine, serine and threonine metabolism	33	4	0.15919	0.79807	1	0.89149	0.2916
Arginine and proline metabolism	38	4	0.22644	0.64505	1	1	0.1673
Glycerolipid metabolism	16	2	0.27631	0.5586	1	1	0.1059
Linoleic acid metabolism	5	1	0.28388	0.54687	1	1	0
Cysteine and methionine metabolism	33	3	0.35947	0.44433	1	1	0.1472
Citrate cycle (TCA cycle)	20	2	0.37367	0.42751	1	1	0.0769
Ether lipid metabolism	20	2	0.37367	0.42751	1	1	0.0843
Biosynthesis of unsaturated fatty acids	36	3	0.41357	0.38345	1	1	0
Ascorbate and aldarate metabolism	8	1	0.4142	0.38279	1	1	0.5
Pentose phosphate pathway	22	2	0.42051	0.37622	1	1	0
Amino sugar and nucleotide sugar metabolism	37	3	0.43132	0.3652	1	1	0.0398
Ubiquinone and other terpenoid-quinone biosynthesis	9	1	0.45219	0.34468	1	1	0
Lysine degradation	25	2	0.48728	0.31222	1	1	0.0047
Caffeine metabolism	10	1	0.48774	0.31181	1	1	0
Biotin metabolism	10	1	0.48774	0.31181	1	1	0
Galactose metabolism	27	2	0.5291	0.27646	1	1	0.0338
Glutathione metabolism	28	2	0.54914	0.26031	1	1	0.0268
alpha-Linolenic acid metabolism	13	1	0.58125	0.23564	1	1	0
Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	14	1	0.60849	0.21574	1	1	0.004
Nicotinate and nicotinamide metabolism	15	1	0.63398	0.19792	1	1	0
Pantothenate and CoA biosynthesis	19	1	0.72052	0.14236	1	1	0
Fatty acid degradation	39	2	0.73006	0.13664	1	1	0
Fructose and mannose metabolism	20	1	0.73877	0.13149	1	1	0
Valine, leucine and isoleucine degradation	40	2	0.74304	0.12899	1	1	0.0108
beta-Alanine metabolism	21	1	0.75584	0.12157	1	1	0
Sphingolipid metabolism	21	1	0.75584	0.12157	1	1	0
Pyruvate metabolism	22	1	0.77181	0.11249	1	1	0.0311
Propanoate metabolism	23	1	0.78675	0.10417	1	1	0
Glycolysis / Gluconeogenesis	26	1	0.82598	0.083029	1	1	0.0002
Phosphatidylinositol signaling system	28	1	0.84808	0.071564	1	1	0.0015
Porphyrin and chlorophyll metabolism	30	1	0.86739	0.061785	1	1	0
Fatty acid elongation	39	1	0.92825	0.032337	1	1	0
Pyrimidine metabolism	39	1	0.92825	0.032337	1	1	0
Tryptophan metabolism	41	1	0.93743	0.02806	1	1	0.1431

Steroid biosynthesis	42	1	0.94158	0.026144	1	1	0.0275
Tyrosine metabolism	42	1	0.94158	0.026144	1	1	0.1397
Fatty acid biosynthesis	47	1	0.95856	0.018379	1	1	0.0147
Purine metabolism	65	1	0.98809	0.0052043	1	1	0
Metabolism of xenobiotics by cytochrome P450	68	1	0.99034	0.0042167	1	1	0.0102
Steroid hormone biosynthesis	85	1	0.99707	0.001273	1	1	0



### HIV– NCs across 3 age groups: Pathway analysis

Pathway	Total	Hits	Raw p	-log10(p)	Holm adjust	FDR	Impact
D-Arginine and D-ornithine metabolism	4	1	0.06057	2.80397207	1	1	0
Linoleic acid metabolism	5	1	0.07515	2.58822924	1	1	0
Glycerophospholipid metabolism	36	2	0.10522	2.25170188	1	1	0.19895
Arginine and proline metabolism	38	2	0.11526	2.16056483	1	1	0.02385
Ascorbate and aldarate metabolism	8	1	0.11761	2.14038121	1	1	0
Valine, leucine and isoleucine biosynthesis	8	1	0.11761	2.14038121	1	1	0
alpha-Linolenic acid metabolism	13	1	0.18426	1.69140748	1	1	0
Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	14	1	0.197	1.62455155	1	1	0.00399
Butanoate metabolism	15	1	0.20955	1.56279291	1	1	0.03175
Histidine metabolism	16	1	0.2219	1.50552845	1	1	0
Pantothenate and CoA biosynthesis	19	1	0.25788	1.35526092	1	1	0
Lysine degradation	25	1	0.32511	1.12359169	1	1	0.15023
Galactose metabolism	27	1	0.34619	1.06076752	1	1	0
Phosphatidylinositol signaling system	28	1	0.35649	1.03144909	1	1	0.03736
Alanine, aspartate and glutamate metabolism	28	1	0.35649	1.03144909	1	1	0.08654
Inositol phosphate metabolism	30	1	0.37663	0.97649201	1	1	0.12939
Arachidonic acid metabolism	36	1	0.4335	0.83586348	1	1	0
Valine, leucine and isoleucine degradation	40	1	0.46861	0.75798441	1	1	0
Fatty acid biosynthesis	47	1	0.52509	0.6441856	1	1	0
Aminoacyl-tRNA biosynthesis	48	1	0.53267	0.62985318	1	1	0
Steroid hormone biosynthesis	85	1	0.74437	0.29521706	1	1	0

**HIV+ NCs across 3 age groups: Pathway analysis**

Pathway	Total	Hits	Raw p	$-\log_{10}(p)$	Holm adjus	FDR	Impact
Glycerophospholipid metabolism	36	2	0.020999	3.86328	1	1	0.19895
Linoleic acid metabolism	5	1	0.031885	3.44562	1	1	0
alpha-Linolenic acid metabolism	13	1	0.081002	2.513281	1	1	0
Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	14	1	0.086981	2.442066	1	1	0.00399
Nicotinate and nicotinamide metabolism	15	1	0.092925	2.375963	1	1	0
Histidine metabolism	16	1	0.098834	2.314314	1	1	0
Glutathione metabolism	28	1	0.16709	1.789223	1	1	0.00709
Arachidonic acid metabolism	36	1	0.20998	1.560743	1	1	0

### HIV+ SCA vs HIV+ NCs: Pathway analysis

Pathway	Total	Hits	Raw p	-log10(p)	Holm adjus	FDR	Impact
Cysteine and methionine metabolism	33	3	0.010281	1.988	0.86362	0.5497	0.13865
Glycerophospholipid metabolism	36	3	0.013088	1.8831	1	0.5497	0.33882
Pantothenate and CoA biosynthesis	19	2	0.028425	1.5463	1	0.7206	0.02143
Sphingolipid metabolism	21	2	0.034316	1.4645	1	0.7206	0.00406
Glutathione metabolism	28	2	0.05819	1.2352	1	0.818	0.01052
Linoleic acid metabolism	5	1	0.069068	1.1607	1	0.818	0
Glyoxylate and dicarboxylate metabolism	32	2	0.073805	1.1319	1	0.818	0.07408
Glycine, serine and threonine metabolism	33	2	0.077903	1.1084	1	0.818	0.21707
Thiamine metabolism	7	1	0.0954	1.0205	1	0.8904	0
Taurine and hypotaurine metabolism	8	1	0.1083	0.96538	1	0.9097	0
Aminoacyl-tRNA biosynthesis	48	2	0.14667	0.83367	1	1	0.16667
alpha-Linolenic acid metabolism	13	1	0.1702	0.76905	1	1	0
Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	14	1	0.18207	0.73975	1	1	0.00399
Glycerolipid metabolism	16	1	0.20534	0.68752	1	1	0.01246
Citrate cycle (TCA cycle)	20	1	0.25	0.60206	1	1	0.09038
beta-Alanine metabolism	21	1	0.26079	0.58372	1	1	0.39925
Propanoate metabolism	23	1	0.28191	0.54989	1	1	0
Alanine, aspartate and glutamate metabolism	28	1	0.33224	0.47855	1	1	0
Phosphatidylinositol signaling system	28	1	0.33224	0.47855	1	1	0.00152
Arachidonic acid metabolism	36	1	0.40582	0.39167	1	1	0
Pyrimidine metabolism	39	1	0.43136	0.36516	1	1	0
Fatty acid biosynthesis	47	1	0.49446	0.30587	1	1	0
Purine metabolism	65	1	0.6129	0.21261	1	1	0.00528

### HIV+ LF vs HIV+ NCs: Pathway analysis

Pathway	Total	Hits	Raw p	$-\log_{10}(p)$	Holm adjus	FDR	Impact
D-Glutamine and D-glutamate metabolism	6	3	0.0004908	3.3091	0.041225	0.04123	0.5
Glycerophospholipid metabolism	36	5	0.0038432	2.4153	0.31898	0.16141	0.39907
Arginine biosynthesis	14	3	0.0075251	2.1235	0.61706	0.18708	0.19289
Alanine, aspartate and glutamate metabolism	28	4	0.0089088	2.0502	0.72161	0.18708	0.44552
Nitrogen metabolism	6	2	0.012493	1.9033	0.99945	0.20988	0
Valine, leucine and isoleucine biosynthesis	8	2	0.022433	1.6491	1	0.31407	0
Butanoate metabolism	15	2	0.073543	1.1335	1	0.88251	0.03175
Pantothenate and CoA biosynthesis	19	2	0.11102	0.95461	1	1	0.02143
Linoleic acid metabolism	5	1	0.14287	0.84507	1	1	0
Aminoacyl-tRNA biosynthesis	48	3	0.17566	0.75532	1	1	0
Glyoxylate and dicarboxylate metabolism	32	2	0.25288	0.59709	1	1	0
Glycine, serine and threonine metabolism	33	2	0.26432	0.57787	1	1	0.14327
Arginine and proline metabolism	38	2	0.32144	0.49291	1	1	0.14386
alpha-Linolenic acid metabolism	13	1	0.33094	0.48026	1	1	0
Pyrimidine metabolism	39	2	0.33277	0.47785	1	1	0
Valine, leucine and isoleucine degradation	40	2	0.34406	0.46336	1	1	0.02168
Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	14	1	0.3514	0.4542	1	1	0.00399
Histidine metabolism	16	1	0.39049	0.40839	1	1	0
Glycerolipid metabolism	16	1	0.39049	0.40839	1	1	0.01246
Ether lipid metabolism	20	1	0.4619	0.33546	1	1	0
beta-Alanine metabolism	21	1	0.47843	0.32019	1	1	0.39925
Propanoate metabolism	23	1	0.51001	0.29242	1	1	0
Galactose metabolism	27	1	0.56766	0.24591	1	1	0
Phosphatidylinositol signaling system	28	1	0.581	0.23582	1	1	0.00152
Glutathione metabolism	28	1	0.581	0.23582	1	1	0.01966
Purine metabolism	65	2	0.59581	0.2249	1	1	0
Porphyrin and chlorophyll metabolism	30	1	0.60649	0.21718	1	1	0
Cysteine and methionine metabolism	33	1	0.6419	0.19253	1	1	0.02089
Arachidonic acid metabolism	36	1	0.67418	0.17122	1	1	0
Tyrosine metabolism	42	1	0.73044	0.13642	1	1	0
Steroid hormone biosynthesis	85	1	0.93226	0.030462	1	1	0

### HIV+ NCI vs HIV+ NCs: Pathway analysis

Pathway	Total	Hits	Raw p	-log10(p)	Holm adjust	FDR	Impact
Alanine, aspartate and glutamate metabolism	28	6	0.001361	2.8662	0.11431	0.07304	0.44552
D-Glutamine and D-glutamate metabolism	6	3	0.001739	2.7597	0.14434	0.07304	0.5
Linoleic acid metabolism	5	2	0.01943	1.7115	1	0.35097	0
Glycerophospholipid metabolism	36	5	0.023001	1.6383	1	0.35097	0.30734
Arachidonic acid metabolism	36	5	0.023001	1.6383	1	0.35097	0.33373
Nitrogen metabolism	6	2	0.028275	1.5486	1	0.35097	0
Butanoate metabolism	15	3	0.029247	1.5339	1	0.35097	0.03175
Histidine metabolism	16	3	0.03482	1.4582	1	0.36561	0.04918
Valine, leucine and isoleucine biosynthesis	8	2	0.049694	1.3037	1	0.46381	0
Ether lipid metabolism	20	3	0.062108	1.2069	1	0.5217	0.08434
Neomycin, kanamycin and gentamicin biosynthesis	2	1	0.090774	1.042	1	0.69318	0
Galactose metabolism	27	3	0.12682	0.89682	1	0.87335	0.06879
Arginine biosynthesis	14	2	0.13516	0.86915	1	0.87335	0.11675
Glyoxylate and dicarboxylate metabolism	32	3	0.18312	0.73727	1	1	0
Pentose and glucuronate interconversions	18	2	0.20228	0.69405	1	1	0.25
Citrate cycle (TCA cycle)	20	2	0.23716	0.62495	1	1	0.07771
Propanoate metabolism	23	2	0.28998	0.53764	1	1	0
Ascorbate and aldarate metabolism	8	1	0.3171	0.49881	1	1	0.5
Glutathione metabolism	28	2	0.37675	0.42394	1	1	0.02675
Caffeine metabolism	10	1	0.3794	0.4209	1	1	0
Aminoacyl-tRNA biosynthesis	48	3	0.38744	0.41179	1	1	0
alpha-Linolenic acid metabolism	13	1	0.46249	0.3349	1	1	0
Glycosylphosphatidylinositol (GPI)-anchor biosynthesis	14	1	0.48767	0.31187	1	1	0.00399
Arginine and proline metabolism	38	2	0.53498	0.27166	1	1	0.086
Valine, leucine and isoleucine degradation	40	2	0.56329	0.24927	1	1	0.02168
Starch and sucrose metabolism	18	1	0.57727	0.23862	1	1	0.4207
Pantothenate and CoA biosynthesis	19	1	0.59714	0.22393	1	1	0
Sphingolipid metabolism	21	1	0.63415	0.19781	1	1	0.15416
Pentose phosphate pathway	22	1	0.65138	0.18617	1	1	0
Glycolysis / Gluconeogenesis	26	1	0.71264	0.14713	1	1	0.00021
Inositol phosphate metabolism	30	1	0.76326	0.11733	1	1	0
Porphyrin and chlorophyll metabolism	30	1	0.76326	0.11733	1	1	0
Glycine, serine and threonine metabolism	33	1	0.79536	0.099438	1	1	0.05034
Purine metabolism	65	2	0.81698	0.08779	1	1	0.01651
Biosynthesis of unsaturated fatty acids	36	1	0.82315	0.08452	1	1	0
Amino sugar and nucleotide sugar metabolism	37	1	0.83156	0.080106	1	1	0.01991
Pyrimidine metabolism	39	1	0.84722	0.072006	1	1	0
Tryptophan metabolism	41	1	0.86143	0.064778	1	1	0
Metabolism of xenobiotics by cytochrome P450	68	1	0.96342	0.016185	1	1	0.0102
Steroid hormone biosynthesis	85	1	0.98439	0.0068345	1	1	0



### HIV+ renal impairment vs HIV+ NCs: Pathway analysis

Pathway	Total	Hits	Raw p	$-\log_{10}(p)$	Holm adjust	FDR	Impact
Glycerophospholipid metabolism	36	3	0.048598	1.3134	1	1	0.24757
Histidine metabolism	16	2	0.051323	1.2897	1	1	0.04918
Linoleic acid metabolism	5	1	0.111	0.9547	1	1	0
Phosphatidylinositol signaling system	28	2	0.13613	0.86604	1	1	0.03888
Alanine, aspartate and glutamate metabolism	28	2	0.13613	0.86604	1	1	0.08654
Ascorbate and aldarate metabolism	8	1	0.17174	0.76513	1	1	0
Arginine and proline metabolism	38	2	0.21996	0.65766	1	1	0.06099
Pyrimidine metabolism	39	2	0.22864	0.64085	1	1	0.14395
alpha-Linolenic acid metabolism	13	1	0.26413	0.57818	1	1	0
Arginine biosynthesis	14	1	0.28136	0.55073	1	1	0.22843
Aminoacyl-tRNA biosynthesis	48	2	0.30739	0.51231	1	1	0.16667
Glycerolipid metabolism	16	1	0.31467	0.50215	1	1	0.01246
Pantothenate and CoA biosynthesis	19	1	0.36182	0.4415	1	1	0
beta-Alanine metabolism	21	1	0.39149	0.40728	1	1	0
Sphingolipid metabolism	21	1	0.39149	0.40728	1	1	0
Galactose metabolism	27	1	0.47268	0.32544	1	1	0
Inositol phosphate metabolism	30	1	0.50922	0.2931	1	1	0.12939
Glyoxylate and dicarboxylate metabolism	32	1	0.5322	0.27393	1	1	0.04233
Cysteine and methionine metabolism	33	1	0.54329	0.26497	1	1	0.02184
Glycine, serine and threonine metabolism	33	1	0.54329	0.26497	1	1	0.21707
Arachidonic acid metabolism	36	1	0.57506	0.24029	1	1	0
Tryptophan metabolism	41	1	0.6233	0.20531	1	1	0.03901

HIV+ NCI vs HIV+ NCs: Pathway analysis

**Sensitivity analysis: NCI patients with moderate fibrosis (FIB4 1.45–<3.25) were excluded.**

Pathway	Total Hits	Raw p	-ln(p)	Holm adjust	FDR	Impact	
Arachidonic acid metabolism	62	4	0.0039017	5.5463	0.31213	0.23256	0.234
D-Glutamine and D-glutamate metabolism	11	2	0.0058139	5.1475	0.4593	0.23256	0.19786
Alanine, aspartate and glutamate metabolism	24	2	0.026769	3.6205	1	0.66754	0.20703
Valine, leucine and isoleucine biosynthesis	27	2	0.033377	3.3999	1	0.66754	0.0885
Glycerophospholipid metabolism	39	2	0.065128	2.7314	1	1	0.00985
Pyrimidine metabolism	60	2	0.13574	1.997	1	1	0
Aminoacyl-tRNA biosynthesis	75	2	0.19328	1.6436	1	1	0
Ether lipid metabolism	23	1	0.22194	1.5054	1	1	0
Sphingolipid metabolism	25	1	0.23882	1.432	1	1	0.1402
Pantothenate and CoA biosynthesis	27	1	0.25535	1.3651	1	1	0.07366
Nitrogen metabolism	39	1	0.34751	1.057	1	1	0
Valine, leucine and isoleucine degradation	40	1	0.35468	1.0366	1	1	0.01657
Histidine metabolism	44	1	0.38258	0.96081	1	1	0.01609
Nicotinate and nicotinamide metabolism	44	1	0.38258	0.96081	1	1	0.01665
Glycine, serine and threonine metabolism	48	1	0.40933	0.89324	1	1	0.09661
Arginine and proline metabolism	77	1	0.57251	0.55772	1	1	0
Tryptophan metabolism	79	1	0.582	0.54128	1	1	0.0478
Purine metabolism	92	1	0.63892	0.44797	1	1	0
Porphyrin and chlorophyll metabolism	104	1	0.68479	0.37864	1	1	0