

Supplement materials

Supplement Table 1 Demographic characteristics of study subjects

	CD (n=9)	HC (n=6)
Female/male	5/4	3/3
Age, years, mean (range)	30.7 (17-43)	27.2 (23-31)
BMI, means (range)	20.9 (19.6-22.3)	21.6 (20.1-23.6)
Sample number	60	14
ileocolitis/colitis	6/3	-
behavioral phynotype	nonstricturing nonpenetrating	-
Medications,no.(%)		-
Thalidomide	2/9	
AZA+Prednisolone	2/9	
AZA	2/9	
Infliximab	3/9	

Supplement Table 2 Differential genus between before and after group treated with different drugs including Thalidomide (Thal), AZA plus Prednisolone, IFX and AZA.

Thal Before vs After

Genus	Mean(Thal_Be%)	std.err(Thal_Be%)	Mean(Thal_Af%)	std.err(Thal_Af%)	P-value
Achromobacter	0	0	1.69E-05	4.74E-06	0.00012
Acetobacteraceae_NA	0	0	4.04E-05	1.84E-05	0.006682

Aeromonadaceae_NA	5.62E-06	3.81E-06	6.55E-05	2.55E-05	0.004208
Brevundimonas	1.16E-05	1.16E-05	0.002431	0.001073	0.005391
Micrococcaceae_NA	0	0	0.000997	0.000394	0.002422
Sediminicola	0	0	1.79E-05	8.20E-06	0.007266
Blautia	0.008731	0.003386	0.001633	0.000897	0.013432
Lactobacillaceae_NA	0	0	0.005605	0.002712	0.012271
Lactobacillus	0	0	0.004604	0.002245	0.012734
Ochrobactrum	3.67E-05	1.30E-05	0.000182	7.03E-05	0.013021
Porphyromonas	0	0	4.53E-05	2.15E-05	0.009375
Blastomonas	0	0	2.08E-05	1.07E-05	0.018245
Caulobacter	0	0	1.02E-05	7.74E-06	0.020894
cc_115	0.000296	0.000189	0.014947	0.007267	0.014776
Methyloversatilis	0	0	1.12E-05	4.26E-06	0.020894
Salinivibrio	0	0	1.13E-05	3.97E-06	0.020894
Sphingobium	0	0	0.001055	0.00054	0.017724
Bifidobacterium	0.022029	0.010092	0.003236	0.001827	0.024193
Corynebacterium	4.10E-06	4.10E-06	0.000817	0.000456	0.029245

Enterococcus	0.000123	0.000123	0.000784	0.000346	0.028057
Halomonadaceae_NA	0	0	3.27E-05	1.81E-05	0.026724
Pseudomonadaceae_NA	9.91E-06	6.40E-06	0.003907	0.002143	0.025411
Klebsiella	0.071057	0.039847	0.000681	0.000132	0.030917
0319-6A21_NA	0	0	7.76E-06	7.76E-06	0.045291
C111_NA	0	0	8.12E-06	5.81E-06	0.045291
Cloacibacillus	0	0	9.22E-06	9.22E-06	0.045291
Faecalibacterium	0.113706	0.054607	0.022316	0.009147	0.041042
Megasphaera	0.000207	0.000117	0.002878	0.001648	0.046255
Planococcaceae_NA	0	0	7.86E-06	7.86E-06	0.045291
Propionibacterium	0	0	0.000165	9.61E-05	0.036146
Rhodobacteraceae_NA	0	0	1.93E-05	1.18E-05	0.041432
Rhodocyclaceae_NA	0	0	9.22E-06	9.22E-06	0.045291
Roseburia	0.000191	3.76E-05	0.000747	0.000337	0.04262

AZA plus Prednisolone Before vs After

Genus	Mean(AZA_Pred_Be%)	std.err(AZA_Pred_Be%)	Mean(AZA_Pred_Af%)	std.err(AZA_Pred_Af%)	P-value
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NA	0.037759	0.01356	0.155119	0.022992	0.000158
Oscillospira	0.000749	0.000556	0.004287	0.000572	0.000147
Thiobacillus	5.62E-05	1.47E-05	0	0	0.00026
Enterobacteriaceae_NA	0.340485	0.081865	0.037666	0.010587	0.000367
Roseomonas	0	0	3.77E-05	1.21E-05	0.000983
Bacillaceae_NA	0.012896	0.005267	1.09E-05	6.37E-06	0.005446
Erysipelotrichaceae_NA	0.000216	0.000116	0.015685	0.006216	0.004751
Lactobacillaceae_NA	0	0	0.019337	0.007814	0.004881
Acinetobacter	0.002161	0.000814	0.071304	0.033583	0.024593
Aggregatibacter	3.33E-06	3.33E-06	3.66E-05	1.56E-05	0.021695
Blautia	0.001057	0.000448	0.013164	0.005728	0.020051
Brevundimonas	0	0	0.008863	0.004211	0.020429
cc_115	1.40E-05	9.79E-06	0.000233	0.000101	0.015802
Collinsella	0.000487	0.000137	0.021543	0.009812	0.017345
Dialister	0.009014	0.004294	7.40E-05	4.15E-05	0.022938
Enterococcus	0	0	0.003895	0.001798	0.015701
Fusobacterium	0.017759	0.007635	0.000217	6.90E-05	0.009452

Herbaspirillum	0	0	5.89E-05	2.69E-05	0.014232
Janthinobacterium	1.66E-05	8.20E-06	0.002078	0.00095	0.015418
Lactobacillus	7.97E-06	4.99E-06	0.022378	0.01058	0.019339
Micrococcaceae_NA	0	0	0.004738	0.002185	0.015469
Paenibacillus	9.24E-05	4.20E-05	1.98E-06	1.98E-06	0.016599
Parabacteroides	0.000193	8.30E-05	0.003792	0.001742	0.02413
Phascolarctobacterium	1.32E-05	8.09E-06	0.002192	0.001044	0.022006
Pirellulaceae_NA	0	0	1.90E-05	9.00E-06	0.019367
Rikenellaceae_NA	8.68E-06	5.34E-06	0.001266	0.000572	0.014056
Sphingomonas	0.000132	8.51E-05	0.010601	0.004752	0.013723
Brachybacterium	0	0	2.29E-05	1.14E-05	0.027893
Coprococcus	0.000409	0.000135	0.00429	0.001924	0.027288
Desulfovibrionaceae_NA	0	0	0.001049	0.000531	0.031362
Actinomyces	9.56E-06	4.17E-06	7.07E-05	3.17E-05	0.03522
Allobaculum	0	0	0.00887	0.004635	0.035271
Bulleidia	0	0	1.51E-05	8.07E-06	0.038944
Lachnospiraceae_NA	0.0356	0.015898	0.102353	0.031887	0.038819

Lactococcus	0	0	0.013746	0.007255	0.037
Arthrospira	0	0	3.76E-05	2.06E-05	0.041836
Bifidobacterium	0.035988	0.01529	0.007977	0.00343	0.045119
Campylobacter	0	0	2.25E-05	1.25E-05	0.043486
Caulobacteraceae_NA	5.44E-05	2.85E-05	0.016911	0.00962	0.046768
Clostridiaceae_NA	0.001362	0.000671	0.009311	0.004295	0.041424
S24-7_NA	3.32E-05	5.45E-06	0.002375	0.001298	0.044407
Vibrio	8.75E-06	8.75E-06	0.002053	0.001163	0.046576
Ruminococcus	4.90E-05	2.27E-05	0.000503	0.000263	0.049469

IFX Before vs After

Genus	Mean(IFX_Be%)	std.err(IFX_Be%)	Mean(IFX_Af%)	std.err(IFX_Af%)	P-value
Acetobacter	0	0	6.70E-05	5.54E-05	0.000999
Adlercreutzia	0	0	0.000469	0.000348	0.000999
Aerococcaceae_NA	0	0	1.67E-05	1.36E-05	0.000999
Aeromicrobium	0	0	1.50E-05	1.50E-05	0.000999
Anoxybacillus	0.001668	0.001668	0	0	0.000999

Azospirillum	0	0	2.00E-05	2.00E-05	0.000999
Corynebacterium	0	0	0.000131	9.37E-05	0.000999
Cupriavidus	0.000415	0.000415	0	0	0.000999
Flavobacteriaceae_NA	0	0	0.000305	0.000301	0.000999
Gaiellaceae_NA	0	0	8.26E-05	7.96E-05	0.000999
Haererehalobacter	0	0	1.37E-05	1.37E-05	0.000999
Haliangiaceae_NA	0	0	2.00E-05	2.00E-05	0.000999
Helicobacteraceae_NA	0	0	1.74E-05	1.18E-05	0.000999
Kaistobacter	0	0	1.32E-05	9.82E-06	0.000999
Kytococcus	7.72E-05	7.58E-05	0	0	0.000999
Lactobacillaceae_NA	0	0	0.00084	0.000833	0.000999
Lactococcus	0	0	2.86E-05	1.85E-05	0.000999
Luteimonas	0.00228	0.002278	0	0	0.000999
Modestobacter	0	0	0.000451	0.000447	0.000999
Nitrospiraceae_NA	0	0	0.000787	0.000787	0.000999
Pirellulaceae_NA	0	0	0.012786	0.01277	0.000999
Plesiomonas	3.06E-05	2.50E-05	0	0	0.000999

Providencia	0	0	0.022768	0.019365	0.000999
Pyramidobacter	0	0	3.04E-05	2.18E-05	0.000999
RFP12_NA	1.59E-05	1.59E-05	0	0	0.000999
Rhodobacteraceae_NA	0	0	0.011255	0.009641	0.000999
Salinivibrio	0	0	2.15E-05	1.80E-05	0.000999
Slackia	0	0	0.000206	0.000121	0.000999
Sphingopyxis	1.68E-05	1.68E-05	0	0	0.000999
Terriglobus	0.000965	0.000963	0	0	0.000999
Thiobacillus	0.034254	0.034254	0	0	0.000999
Desulfovibrionaceae_NA	0	0	1.29E-05	8.53E-06	0.001914
Rothia	0	0	1.41E-05	8.36E-06	0.001914
Filifactor	0	0	1.91E-05	1.91E-05	0.004186
Methylopila	0	0	9.40E-06	9.40E-06	0.004186
Haemophilus	0.015797	0.00706	0.000677	0.000281	0.004995
Ralstonia	0.010555	0.006346	0.00028	9.81E-05	0.004995
Pseudomonas	0.016248	0.006064	0.000271	7.75E-05	0.005994
Dermacoccus	0.013478	0.010929	0.000142	2.68E-05	0.006993

Roseburia	0.000338	0.000128	0.038008	0.011925	0.008991
Xanthomonadaceae_NA	1.40E-05	1.01E-05	0	0	0.009432
Micrococcus	2.49E-06	2.49E-06	0.00036	0.000252	0.00999
Desulfovibrio	1.24E-06	1.24E-06	1.65E-05	9.55E-06	0.014305
Neisseria	1.38E-06	1.38E-06	1.30E-05	1.00E-05	0.014305
Fusobacterium	0.028799	0.011677	0.001951	0.000745	0.014985
Streptococcus	0.005078	0.002327	0.000562	0.000208	0.014985
Ruminococcus	5.59E-05	2.60E-05	0.014601	0.008781	0.017982
Acetobacteraceae_NA	0	0	8.53E-06	8.53E-06	0.020011
Allobaculum	0	0	7.94E-06	5.32E-06	0.020011
Brachybacterium	0	0	6.34E-06	5.01E-06	0.020011
Synechococcus	0	0	8.53E-06	8.53E-06	0.020011
Veillonellaceae_NA	0	0	8.07E-06	6.78E-06	0.020011
Anaerostipes	4.35E-06	4.35E-06	0.000593	0.00042	0.027972
Morganella	8.98E-06	4.19E-06	0.000235	0.000132	0.027972
cc_115	0.012135	0.004774	0.000561	0.0003	0.028971
Peptostreptococcus	0.010646	0.005233	0.000212	4.30E-05	0.031968

Leuconostocaceae_NA	0	0	6.82E-06	6.82E-06	0.043755
NB1-i_NA	0	0	6.82E-06	6.82E-06	0.043755
Pasteurella	0	0	6.23E-06	4.64E-06	0.043755
Pseudonocardia	2.34E-05	1.73E-05	1.25E-06	1.25E-06	0.04525

AZA Before vs After

Genus	Mean(AZA_Be%)	std.err(AZA_Be%)	Mean(AZA_Af%)	std.err(AZA_Af%)	P-value
Enterobacteriaceae_NA	0.193528	0.025244	0.078448	0.013783	0.000358
Aggregatibacter	0.000895	0.000394	2.72E-05	1.10E-05	0.012947
Bacteroides	0.139369	0.029156	0.060236	0.023357	0.020503
Cetobacterium	0	0	0.000106	4.95E-05	0.018079
Cloacibacillus	2.07E-06	2.07E-06	0.000232	0.00011	0.021232
Comamonadaceae_NA	0.004324	0.001885	0.000121	7.59E-05	0.011808
Coprococcus	0.001521	0.000408	0.013083	0.005211	0.012616
Eggerthella	0.000376	0.000241	0.001849	0.000617	0.012126
Fusobacteriaceae_NA	0.047021	0.021012	0.000458	0.000182	0.01251
Helicobacteraceae_NA	0	0	1.05E-05	5.79E-06	0.020114

Lactococcus	0	0	0.000326	0.000152	0.016735
Oxalobacteraceae_NA	0	0	2.50E-05	8.70E-06	0.00298
Roseburia	0.003185	0.001398	0.071319	0.027475	0.006821
Ruminococcaceae_NA	0.025066	0.011322	0.055881	0.007791	0.010947
Salmonella	0	0	1.50E-05	6.97E-06	0.015185
Nocardiodaceae_NA	0	0	2.25E-05	1.11E-05	0.024993
Achromobacter	0	0	8.02E-06	8.02E-06	0.043934
Bulleidia	0.000536	0.000275	3.68E-06	3.68E-06	0.030775
Caulobacteraceae_NA	0.000145	5.73E-05	3.68E-05	1.79E-05	0.039278
Comamonas	0.003926	0.002105	2.74E-05	1.32E-05	0.036272
Halomicronema	0	0	9.45E-06	9.45E-06	0.043934
Lachnospira	0.000216	0.000209	0.003085	0.001581	0.039808
Morganella	0.005935	0.003024	0.000144	0.000131	0.032417
Proteus	0.002807	0.001584	0	0	0.04204
Sediminicola	0	0	8.12E-06	5.96E-06	0.043934
Serratia	0	0	1.50E-05	1.10E-05	0.043934
Adlercreutzia	0	0	0.000346	0.000202	0.046298

Supplement Table 3 Differential predicted KEGG pathways (level 3) among before, after and HC group. The means and p value were calculated.

labels	Before	After	HC	p_value
ABC transporters	3520.538	3729.441	4053.571	0.035308
DNA repair and recombination proteins	2289.346	2628.382	3004.429	0.003966
Ribosome	1727.962	2034.235	2379.786	0.001193
Purine metabolism	1883.077	2115.941	2345.714	0.009094
Peptidases	1618.077	1816.824	2020	0.010854
Pyrimidine metabolism	1432.269	1614.147	1883.643	0.007393
Chromosome	1308.346	1475.235	1655.214	0.008431
Amino acid related enzymes	1212.385	1395.588	1545.071	0.014886
Amino sugar and nucleotide sugar metabolism	1197.5	1313.941	1506.5	0.023218
Ribosome Biogenesis	1176.731	1325.676	1472.571	0.014813
Methane metabolism	1084.346	1245.206	1453	0.015512
Arginine and proline metabolism	1098.192	1246.176	1353.357	0.028433
Oxidative phosphorylation	1029.808	1214.853	1303.857	0.008016
DNA replication proteins	964.154	1104.441	1288.214	0.005005
Glycolysis / Gluconeogenesis	1022.192	1137.824	1264.786	0.016175
Porphyrin and chlorophyll metabolism	907.385	1090.471	1258.357	0.004948
Pyruvate metabolism	1015.615	1127.265	1205.429	0.025241
Aminoacyl-tRNA biosynthesis	864.462	1036.235	1198.714	0.000583
Alanine, aspartate and glutamate metabolism	884.538	1014.147	1146.571	0.012551
Chaperones and folding catalysts	918.577	1020.235	1062.429	0.015806

Starch and sucrose metabolism	818.577	937.559	1039.214	0.037482
Cysteine and methionine metabolism	836.808	912.324	1035.214	0.029155
Pentose phosphate pathway	786.462	871	1019.429	0.011037
Transcription machinery	737.692	869.559	1013.5	0.003011
Lysine biosynthesis	668	801.765	945.286	0.006984
Homologous recombination	711.192	820.618	941.143	0.003686
Phenylalanine, tyrosine and tryptophan biosynthesis	676.231	795.912	928.786	0.005293
Mismatch repair	631.038	736.971	882.786	0.001613
Peptidoglycan biosynthesis	648.5	737.529	835.857	0.01384
Valine, leucine and isoleucine biosynthesis	614.923	727.118	801	0.006825
Butanoate metabolism	696.808	773.882	735.214	0.034034
Carbon fixation in photosynthetic organisms	565.5	628.706	709.786	0.012001
DNA replication	514.115	588.118	686.429	0.004771
Pantothenate and CoA biosynthesis	523.038	619.824	673.429	0.01211
Histidine metabolism	491.962	574.912	650.429	0.005968
Lipid biosynthesis proteins	538	629.971	649.357	0.012475
Glycerophospholipid metabolism	503.538	574.147	638.857	0.00797
Propanoate metabolism	586.192	677.882	633.286	0.029443
One carbon pool by folate	481.769	550.471	631	0.004085
Protein export	474.385	547.647	623.286	0.00219
Glyoxylate and dicarboxylate metabolism	572.885	636.971	609.714	0.02368
Terpenoid backbone biosynthesis	439.731	521.235	602.357	0.000632
Cell cycle - Caulobacter	407.269	507.206	584.643	0.000367
Photosynthesis proteins	384.308	540.147	579.929	0.003316
Translation factors	409.923	477.353	549.929	0.002386

Fatty acid biosynthesis	425.154	501.382	548.786	0.005228
Thiamine metabolism	395.231	466.029	537.214	0.007066
Photosynthesis	349.846	485.618	530.857	0.003248
Glycerolipid metabolism	369.308	411.147	503.929	0.006025
RNA degradation	387.308	439.588	494.857	0.002744
Nicotinate and nicotinamide metabolism	387.115	430.676	458.357	0.01195
Base excision repair	355.346	403.441	455.071	0.003002
Nucleotide excision repair	288.231	342.794	421.429	0.000608
Cytoskeleton proteins	262.692	327.471	414	0.0008
Folate biosynthesis	366.192	417.118	411.429	0.0451
Selenocompound metabolism	337.346	381	401.857	0.022626
Bacterial chemotaxis	275.808	345.265	378.786	0.002503
Sulfur relay system	301.5	336.412	341.071	0.0281
C5-Branched dibasic acid metabolism	275.846	312.235	330.5	0.031997
Prenyltransferases	248.846	294.853	318.786	0.000849
Streptomycin biosynthesis	237.231	266.294	287.5	0.029443
Sulfur metabolism	254.769	285.294	285.714	0.04737
Lipopolysaccharide biosynthesis proteins	408.154	356.794	265	0.017081
Chloroalkane and chloroalkene degradation	194.154	238.353	243.5	0.013393
Riboflavin metabolism	217.385	244.294	227.071	0.013998
Vitamin B6 metabolism	181.231	195.382	205.571	0.034595
Sphingolipid metabolism	138.385	155.382	197.929	0.032463
Tetracycline biosynthesis	134	159.176	190.286	0.002788
Polyketide sugar unit biosynthesis	138.308	160.029	184.929	0.00477
RNA polymerase	125.385	151.147	179.143	0.000401

Tuberculosis	120.615	153.294	172.429	0.00022
Plant-pathogen interaction	120.115	147.765	169.214	0.001326
RNA transport	111.654	131.647	159.214	0.015354
Lipopolysaccharide biosynthesis	249.462	225.088	159	0.040459
D-Glutamine and D-glutamate metabolism	125.462	139.882	153.286	0.008418
Novobiocin biosynthesis	120.423	135.382	147.143	0.045193
Phenylpropanoid biosynthesis	112.192	133.824	147.143	0.044184
Bacterial toxins	91.538	97.529	134.071	0.000637
Taurine and hypotaurine metabolism	106.385	115.265	118.786	0.049265
Polycyclic aromatic hydrocarbon degradation	89.077	111.471	111.071	0.041232
Glutamatergic synapse	83.231	98.029	109.357	0.011895
D-Alanine metabolism	90.692	96.147	108.071	0.024845
Bisphenol degradation	77.692	96.765	101.929	0.022401
Insulin signaling pathway	70.308	85.971	101.429	0.001358
Xylene degradation	60.615	69.118	80.643	0.021077
Linoleic acid metabolism	55.885	71.529	76.571	0.007404
Butirosin and neomycin biosynthesis	48.538	56.618	65.929	0.025935
Protein processing in endoplasmic reticulum	46.615	55.412	60.5	0.000879
Type I diabetes mellitus	43.385	51.353	53.786	0.001201
Pathways in cancer	45.269	56.176	53.571	0.002153
Biosynthesis of vancomycin group antibiotics	41.462	47.118	53.286	0.003813
Type II diabetes mellitus	41.038	47.441	52.357	0.00502
Zeatin biosynthesis	36.538	41.647	47.571	0.005057
Proteasome	34.654	40.706	43.714	0.015841
NOD-like receptor signaling pathway	32.846	38.735	43.357	0.00894

Prostate cancer	33.423	38.618	42.929	0.018885
Antigen processing and presentation	32.385	38.412	42.786	0.009035
Progesterone-mediated oocyte maturation	32.385	38.412	42.786	0.009035
Primary bile acid biosynthesis	21.692	27.794	33.714	0.016442

Supplement figure legends

Figure S1 The Crohn's Disease Activity Index (CDAI) were significantly declined in patients after treatment.

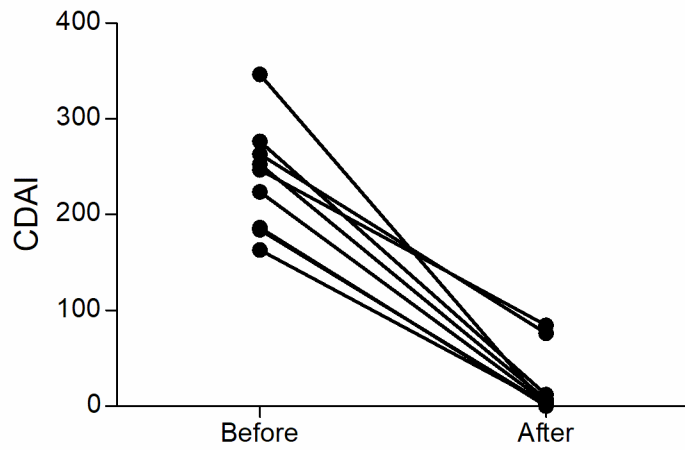
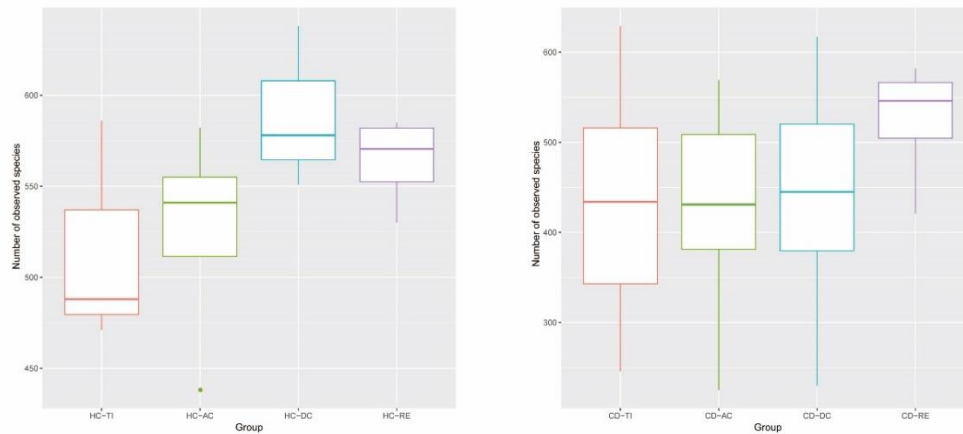


Figure S2 Alpha diversity analysis comparing among different regions of intestinal tract in both patients with CD and healthy controls (HC). Boxplot of observed species (A) and Shannon index (B) in ileum (TI), ascending colon (AC), descending colon (DC) and rectum (RE). The boxes indicate interquartile ranges (IQRs) and the median (middle line).

A



B

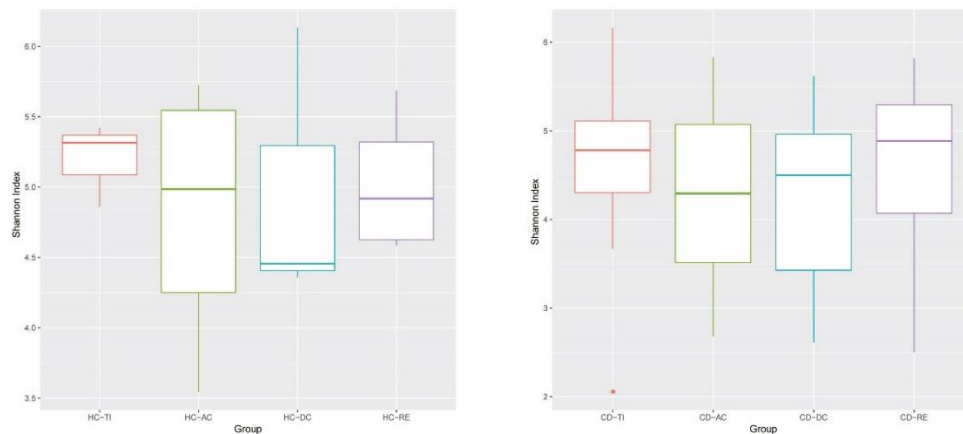


Figure S3 Alpha diversity analysis comparing between patients before and after treatment with different medications. Boxplot of observed species (A) and Chao1 index (B) in thalidomide (Thal), azathioprine plus prednisolone (AZA_Pred), infliximab (IFX) and azathioprine (AZA). The boxes indicate interquartile ranges (IQRs) and the median (middle line).

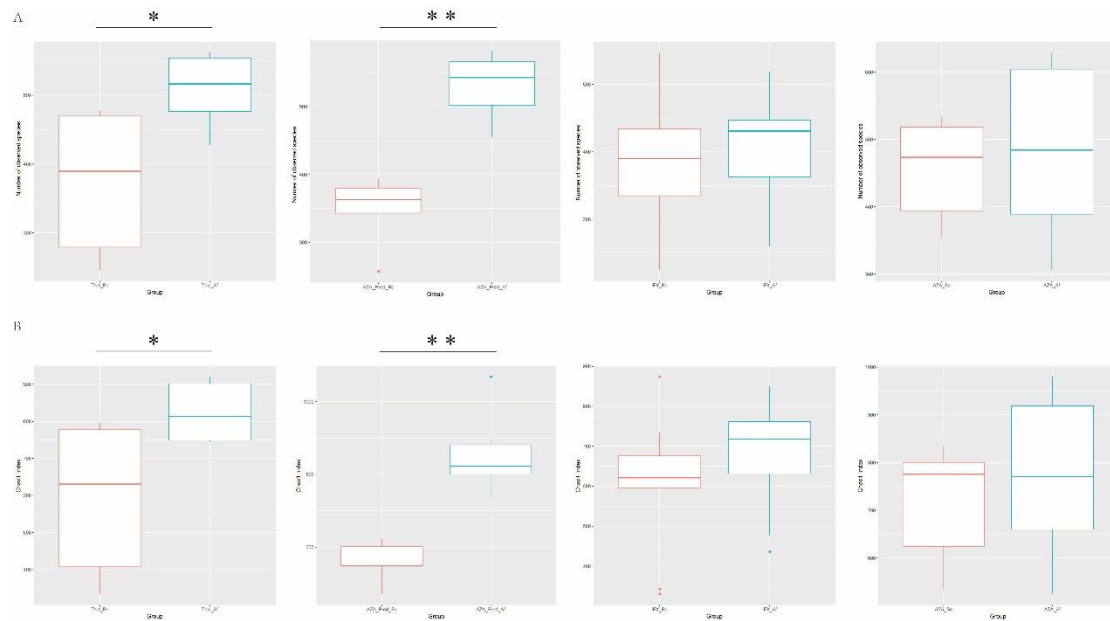


Figure S4 Pathways predicted to show significant different abundances among healthy controls (HC) and patients with CD before and after treatment according to Kyoto Encyclopedia of Genes and Genome (KEGG) pathway analysis.

