

1 Supplementary Data

All relevant data are contained within the article and supplementary material (**Supplementary Data 2**). Any further details are available upon request.

2 Supplementary Tables

Supplementary Table S1. Gating strategy for immune cell populations detected by mass cytometry.

Immune Cell Population	Gating Strategy	Passed Filtering?	Lineage Parent Population
Granulocytes	CD45loCD66b+	YES	Live, Singlets
Neutrophils	CD45loCD66b+, CD294-CD16+	YES	Granulocytes
Eosinophils	CD45loCD66b+, CD294+CD16-	YES	Granulocytes
Basophils	CD45+CD66b-, CD19-CD20-, CD3-CD56-, HLA-DR-CD11c-, CD123+CD294+	YES	Granulocytes
Lymphocytes	CD45+CD66b-	YES	Live, Singlets
Total B Cells	CD45+CD66b-, CD56-CD14-, CD19+CD3-	YES	Lymphocytes
Naive B Cells	CD45+CD66b-, CD56-CD14-, CD19+CD3-, CD19+CD27-	YES	Total B Cells
Total Memory B Cells	CD45+CD66b-, CD56-CD14-, CD19+CD3-, CD19+CD27+	YES	Total B Cells
Plasmablasts	CD45+CD66b-, CD56-CD14-, CD19+CD3-, CD19+CD27+, CD38+CD20-	NO	Total B Cells
Naive B Cells (IgD+/-)	CD45+CD66b-, CD56-CD14-, CD19+CD3-, CD27-IgD+/-	YES	Total B Cells
IgD- Memory B Cells	CD45+CD66b-, CD56-CD14-, CD19+CD3-, CD27+IgD-	YES	Total B Cells
IgD+ Memory B Cells	CD45+CD66b-, CD56-CD14-, CD19+CD3-, CD27+IgD+	NO	Total B Cells
Total Monocytes	CD45+CD66b-, CD19-CD20-, CD3-CD56-, CD11c+HLA-DR+, CD14+/-CD11c+	YES	Lymphocytes
Classical Monocytes	CD45+CD66b-, CD19-CD20-, CD3-CD56-, CD11c+HLA-DR+, CD14+/-CD11c+, CD38+CD14hi, CD14hiCD16lo/-	YES	Total Monocytes
Transitional Monocytes	CD45+CD66b-, CD19-CD20-, CD3-CD56-, CD11c+HLA-DR+, CD14+/-CD11c+, CD38lo/-CD14int, CD14intCD16+	YES	Total Monocytes
Nonclassical Monocytes	CD45+CD66b-, CD19-CD20-, CD3-CD56-, CD11c+HLA-DR+, CD14+/-CD11c+, CD38-CD14-, CD14-CD16+	YES	Total Monocytes
mDC	CD45+CD66b-, CD19-CD20-, CD3-CD14-, HLA-DR+, CD123-CD11c+, CD38+	YES	mDC + pDC
pDC	CD45+CD66b-, CD19-CD20-, CD3-CD14-, HLA-DR+, CD123+CD11c-	NO	mDC + pDC
Total NK	CD45+CD66b-, CD19-CD20-, CD3-CD14-, CD45RA+CD123-, CD45+CD56+	YES	Lymphocytes
Late NKs	CD45+CD66b-, CD19-CD20-, CD3-CD14-, CD45RA+CD123-, CD45+CD56+, CD56+CD57+	YES	Total NK
Early NKs	CD45+CD66b-, CD19-CD20-, CD3-CD14-, CD45RA+CD123-, CD45+CD56+, CD56+CD57-	YES	Total NK

Immune Cell Population	Gating Strategy	Passed Filtering?	Lineage Parent Population
Total T Cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+	YES	Lymphocytes
Gamma Delta T Cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD4-CD8-, CD3+TCR $\gamma\delta$ +	YES	Total T Cells
MAIT / NKT Cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD3+CD4-, CD28+CD161hi	YES	Total T Cells
CD3+ ab T cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -	YES	Total T Cells
CD8 ab T Cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4-CD8+, CD8+CD161lo/-	YES	Total T Cells
CD8 Naive	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4-CD8+, CD8+CD161lo/-, CD8+CCR7hi, CD45RA+CD45RO-	YES	CD8 ab T Cells
CD8 Central Memory	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4-CD8+, CD8+CD161lo/-, CD8+CCR7hi, CD45RA-CD45RO+	NO	CD8 ab T Cells
CD8 Effector Memory	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4-CD8+, CD8+CD161lo/-, CD8+CCR7lo/-, CD8+CD27+	YES	CD8 ab T Cells
CD8 Terminal Effector	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4-CD8+, CD8+CD161lo/-, CD8+CCR7lo/-, CD8+CD27-	YES	CD8 ab T Cells
TEMRA CD8+ T cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4-CD8+, CD8+CD161lo/-, CD45RA+CCR7-, CD28-CCR7-	YES	CD8 ab T Cells
Activated CD8+ T cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4-CD8+, CD8+CD161lo/-, HLA-DR+CD38+	YES	CD8 ab T Cells
Activated, Senescent CD8+ T cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4-CD8+, CD8+CD161lo/-, HLA-DR+CD38+, CD28-	NO	CD8 ab T Cells
Exhausted CD8+ T cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4-CD8+, CD8+CD161lo/-, CD8+CD28-, PD-1+TIGIT+	NO	CD8 ab T Cells
CD4 ab T Cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4+CD8-	YES	Total T Cells
CD4 Naive	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4+CD8-, CD4+CCR7hi, CD45RA+CD45RO-	YES	CD4 ab T Cells
CD4 Central Memory	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4+CD8-, CD4+CCR7hi, CD45RA-CD45RO+	YES	CD4 ab T Cells
CD4 Effector Memory	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4+CD8-, CD4+CCR7lo/-, CD45RA-CD45RO+, CD45RO+CD27+	YES	CD4 ab T Cells
CD4 Terminal Effectors	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4+CD8-, CD4+CCR7lo/-, CD45RA-CD45RO+, CD45RO+CD27-	YES	CD4 ab T Cells
Th1-like	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4+CD8-, CD4+CCR4-, CD45RA-CD45RO+, CXCR3+CCR6-	YES	CD4 ab T Cells
Th2-like	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4+CD8-, CD4+CXCR5-, CD45RA-CCR4+, CXCR3-CCR6-	YES	CD4 ab T Cells
Th17-like	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4+CD8-, CD4+CXCR5-, CD45RA-CCR4+, CXCR3-CCR6+	YES	CD4 ab T Cells
Treg	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4+CD8-, CD4+CCR4+, CD45RA-CD45RO+, CD25hiCD127lo/-	YES	CD4 ab T Cells
Activated CD4+ T cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4+CD8-, HLA-DR+CD38+	YES	CD4 ab T Cells
Activated, Senescent CD4+ T cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4+CD8-, HLA-DR+CD38+, CD28-	NO	CD4 ab T Cells
Exhausted CD4+ T cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4+CD8-, CD28-, PD-1+TIGIT+	NO	CD4 ab T Cells
TEMRA CD4+ T cells	CD45+CD66b-, CD19-CD20-, CD14-CD11c-, CD45+CD3+, CD3+TCR $\gamma\delta$ -, CD4+CD8-, CD45RA+CCR7-, CD28-	NO	CD4 ab T Cells

Supplementary Table S2. Antibody clones and mass tags used for mass cytometry experiments.

Antibody	Clone	Mass	Kit Cat. No.
CD279/PD-1	EH12.2H7	175Lu	201405
TIGIT	MBSA43	209Bi	201405
CD45	HI30	89Y	201325
CD196/CCR6	G034E3	141Pr	201325
CD123	6H6	143Nd	201325
CD19	HIB19	144Nd	201325
CD4	RPA-T4	145Nd	201325
CD8a	RPA-T8	146Nd	201325
CD11c	Bu15	147Sm	201325
CD16	3G8	148Nd	201325
CD45RO	UCHL1	149Sm	201325
CD45RA	HI100	150Nd	201325
CD161	HP-3G10	151Eu	201325
CD194/CCR4	L291H4	152Sm	201325
CD25	BC96	153Eu	201325
CD27	O323	154Sm	201325
CD57	HCD57	155Gd	201325
CD183/CXCR3	G025H7	156Gd	201325
CD185/CXCR5	J252D4	158Gd	201325
CD28	CD28.2	160Gd	201325
CD38	HB-7	161Dy	201325
CD56/NCAM	NCAM16.2	163Dy	201325
TCR $\gamma\delta$	B1	164Dy	201325
CD294	BM16	166Er	201325
CD197/CCR7	G043H7	167Er	201325
CD14	63D3	168Er	201325
CD3	UCHT1	170Er	201325
CD20	2H7	171Yb	201325
CD66b	G10F5	172Yb	201325
HLA-DR	LN3	173Yb	201325
IgD	IA6-2	174Yb	201325
CD127	A019D5	176Yb	201325
Cell-ID Intercalator	N/A	103Rh	201325

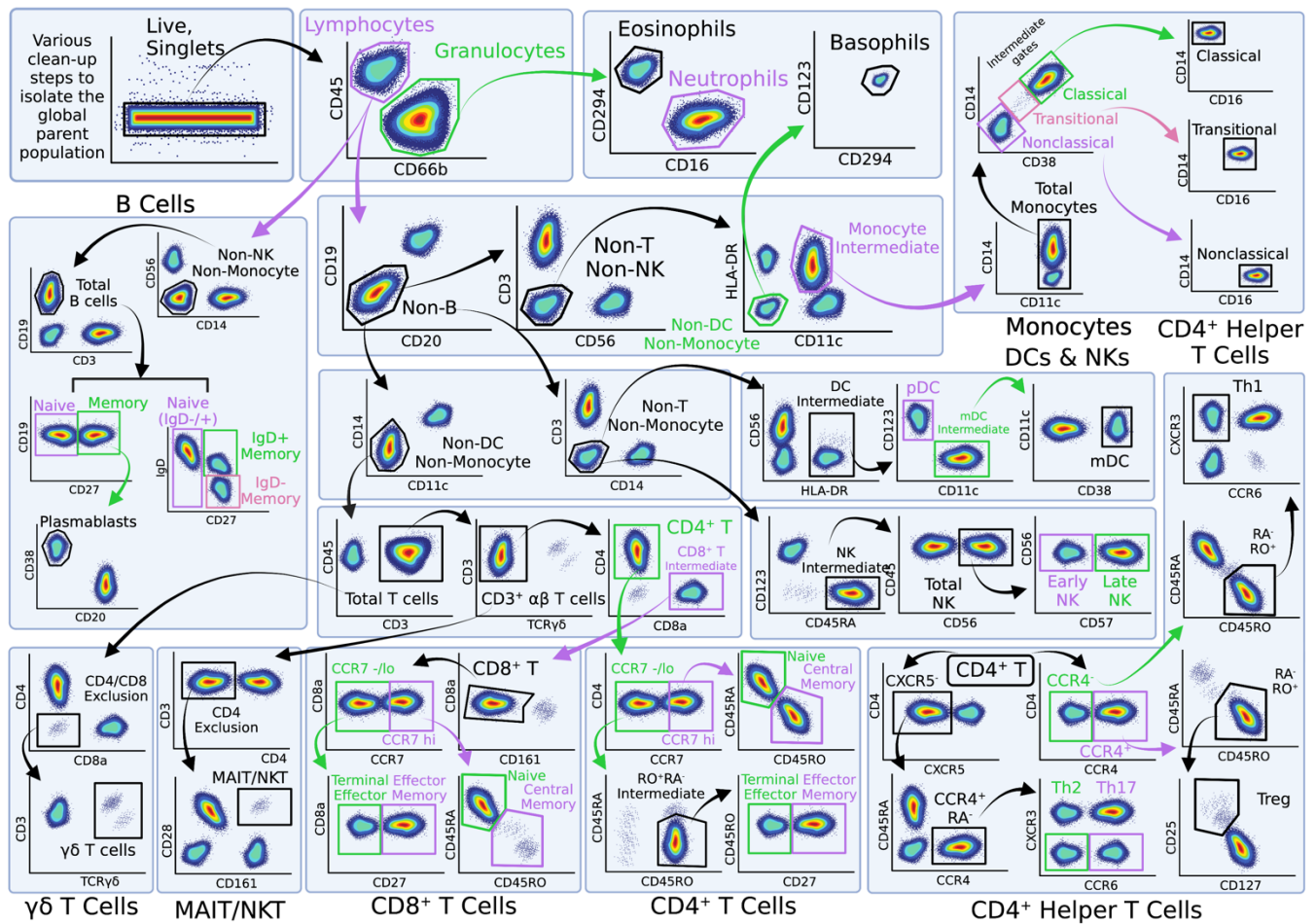
Supplementary Table S3. Results of ANCOVA and Two-Way ANOVA for comparison of inflammatory mediators and cellular immunophenotypes across the groups. If the p-value correction resulted in a $p > 1$, then the p was set to 1.

Variable	HIV-CON		IDU-CON		DP-CON		IDU-HIV		DP-HIV		DP-IDU		HIV		IDU		Interaction	
	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Coefficient Estimate	2-Way ANOVA p-value	Coefficient Estimate	2-Way ANOVA p-value	Coefficient Estimate	2-Way ANOVA p-value
4E.BP1	0.2703	1	0.1628	1	-0.1383	1	-0.1075	1	-0.4086	1	-0.3011	1	0.2703	1	0.1628	1	0.0172	0.4972
ADA	0.2028	1	0.3060	1	0.3486	1	0.1032	1	0.1458	1	0.0426	1	0.2028	0.9095	0.3060	0.5800	0.0057	1
AXIN1	-0.1976	1	-0.2490	1	-0.8637	0.1837	-0.0514	1	-0.6660	0.2320	-0.6146	0.2729	-0.1976	1	-0.2490	1	0.0032	1
CASP.8	0.5246	0.2783	0.0411	1	0.1118	1	-0.4835	0.1521	-0.4129	0.8241	0.0706	1	0.5246	0.1486	0.0411	1	0.0134	0.6963
CCL11	0.5192	0.0171	0.5734	0.0419	0.4789	0.2129	0.0542	1	-0.0403	1	-0.0945	1	0.5192	0.0111	0.5734	0.0209	0.0174	0.0603
CCL19	1.0558	0.0243	0.9890	0.1583	1.2556	0.0539	-0.0668	1	0.1998	1	0.2666	1	1.0558	0.0152	0.9890	0.0792	-0.0004	1
CCL20	1.5864	0.0018	2.0134	0.0013	2.2862	0.0004	0.4270	1	0.6998	0.7813	0.2728	1	1.5864	0.0015	2.0134	0.0007	0.0019	1
CCL23	0.4326	0.3220	0.3117	1	0.4287	0.8631	-0.1209	1	-0.0038	1	0.1170	1	0.4326	0.1708	0.3117	0.7400	-0.0080	1
CCL25	0.4167	0.2370	0.3592	0.8407	0.7660	0.0229	-0.0575	1	0.3493	0.6110	0.4068	0.2749	0.4167	0.1275	0.3592	0.4204	0.0110	0.5999
CCL28	0.1038	1	0.0546	1	-0.0294	1	-0.0492	1	-0.1332	1	-0.0840	1	0.1038	1	0.0546	1	0.0121	0.1250
CCL3	0.7862	0.0426	0.8466	0.1024	1.0098	0.0493	0.0604	1	0.2237	1	0.1632	1	0.7862	0.0255	0.8466	0.0512	0.0280	0.0756
CCL4	0.2156	1	0.2747	1	0.3750	1	0.0591	1	0.1595	1	0.1003	1	0.2156	1	0.2747	1	0.0067	1
CD244	0.2408	0.5623	-0.0485	1	0.2628	0.9732	-0.2894	0.0866	0.0220	1	0.3113	0.1899	0.2408	0.2919	-0.0485	1	0.0039	1
CD40	-0.0231	1	0.0422	1	0.0645	1	0.0653	1	0.0876	1	0.0223	1	-0.0231	1	0.0422	1	0.0136	0.0280
CD5	0.4609	0.0764	0.2706	1	0.5334	0.1654	-0.1903	1	0.0725	1	0.2629	0.9343	0.4609	0.0439	0.2706	0.6699	-0.0092	0.7184
CD6	0.6468	0.0477	0.1940	1	0.8965	0.0296	-0.4528	0.1419	0.2496	1	0.7025	0.0279	0.6468	0.0283	0.1940	1	-0.0035	1
CD8A	1.0174	0.0003	0.5030	0.5898	0.9482	0.0246	-0.5144	0.0802	-0.0691	1	0.4453	0.4737	1.0174	0.0004	0.5030	0.2949	0.0037	1
CDCP1	0.8642	0.0103	1.1226	0.0058	1.7255	0.0000	0.2584	1	0.8613	0.0184	0.6029	0.1809	0.8642	0.0070	1.1226	0.0029	0.0211	0.2192
CSF.1	0.2690	0.0152	0.3758	0.0039	0.4018	0.0034	0.1068	0.8448	0.1327	0.9471	0.0259	1	0.2690	0.0100	0.3758	0.0019	0.0038	0.9534
CST5	0.0729	1	-0.1281	1.0000	0.2669	1	-0.2010	1	0.1940	1	0.3950	0.1888	0.0729	1	-0.1281	1	0.0086	0.8005
CX3CL1	0.2724	0.4544	0.4528	0.0912	0.5452	0.0396	0.1804	0.8903	0.2728	0.5509	0.0924	1	0.2724	0.2377	0.4528	0.0456	0.0094	0.4530
CXCL1	-0.0980	1	0.1281	1	-0.9319	0.1804	0.2261	1	-0.8339	0.0964	-1.0600	0.0097	-0.0980	1	0.1281	1	0.0239	0.2636
CXCL10	1.2558	0.0203	0.8323	0.6417	1.5228	0.0397	-0.4236	1	0.2670	1	0.6906	0.6477	1.2558	0.0130	0.8323	0.3209	0.0317	0.2479
CXCL11	1.0539	0.1179	0.8574	0.6900	1.0547	0.4463	-0.1965	1	0.0008	1	0.1972	1	1.0539	0.0659	0.8574	0.3450	0.0113	1
CXCL5	0.1488	1	0.2665	1	-0.5958	1	0.1177	1	-0.7446	0.4182	-0.8623	0.1683	0.1488	1	0.2665	1	0.0409	0.0434
CXCL6	0.0928	1	0.3429	1	-0.0815	1	0.2501	1	-0.1743	1	-0.4245	1	0.0928	1	0.3429	1	0.0159	0.7492
CXCL9	1.4044	0.0001	0.6061	0.6851	1.2419	0.0174	-0.7983	0.0154	-0.1625	1	0.6358	0.2844	1.4044	0.0001	0.6061	0.3426	0.0210	0.3653
DNER	-0.0190	1	0.1503	0.9151	0.1487	1	0.1693	0.1105	0.1677	0.4136	-0.0017	1	-0.0190	1	0.1503	0.4575	-0.0001	1
EN.RAGE	0.0555	1	0.1267	1	0.2499	1	0.0712	1	0.1944	1	0.1231	1	0.0555	1	0.1267	1	0.0112	0.8268
FGF.19	0.0448	1	0.1985	1	0.4318	1	0.1537	1	0.3871	1	0.2334	1	0.0448	1	0.1985	1	-0.0115	1
FGF.21	0.5891	1	-0.0076	1	0.1941	1	-0.5967	1	-0.3951	1	0.2017	1	0.5891	0.8389	-0.0076	1	-0.0192	1
FIt3L	0.2893	0.7518	0.3870	0.5339	0.7881	0.0085	0.0977	1	0.4988	0.0736	0.4011	0.2100	0.2893	0.3868	0.3870	0.2669	0.0172	0.1007
GDNF	0.0344	1	0.2814	1	0.2673	1	0.2471	0.5323	0.2329	1	-0.0141	1	0.0344	1	0.2814	0.5639	0.0077	0.9291
HGF	0.2385	1	0.4551	0.5147	0.6111	0.2010	0.2166	1	0.3727	0.6472	0.1560	1	0.2385	0.8420	0.4551	0.2574	0.0153	0.3088
IFN.gamma	1.0689	0.0339	1.3693	0.0228	1.1962	0.1075	0.3004	1	0.1273	1	-0.1731	1	1.0689	0.0207	1.3693	0.0114	0.0048	1

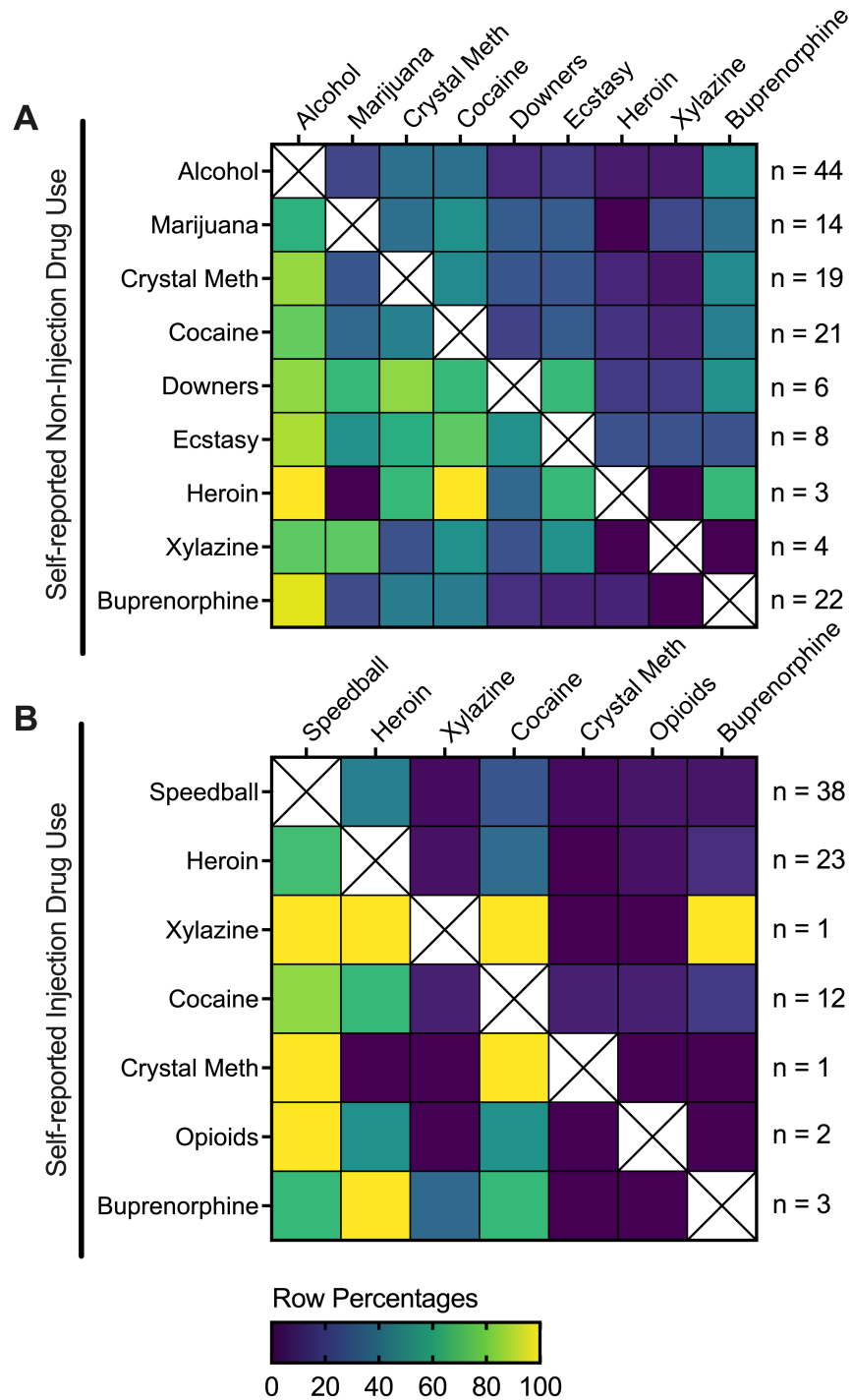
Variable	HIV-CON		IDU-CON		DP-CON		IDU-HIV		DP-HIV		DP-IDU		HIV		IDU		Interaction	
	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Coefficient Estimate	2-Way ANOVA p-value	Coefficient Estimate	2-Way ANOVA p-value	Coefficient Estimate	2-Way ANOVA p-value
IL.10RA	0.1890	1	0.2637	1	0.2627	1	0.0747	1	0.0737	1	-0.0009	1	0.1890	1	0.2637	0.8180	-0.0004	1
IL.10RB	0.3195	0.0437	0.4165	0.0256	0.4995	0.0080	0.0971	1	0.1801	0.9095	0.0830	1	0.3195	0.0262	0.4165	0.0128	0.0080	0.3477
IL.12B	0.5135	0.7185	0.2588	1	0.5754	1	-0.2547	1	0.0619	1	0.3166	1	0.5135	0.3702	0.2588	1	0.0046	1
IL.15RA	0.3510	0.0209	0.2525	0.4889	0.5817	0.0013	-0.0985	1	0.2307	0.4124	0.3293	0.0420	0.3510	0.0133	0.2525	0.2445	0.0037	1
IL.17A	0.5165	0.0705	0.7398	0.0195	0.7332	0.0376	0.2232	1	0.2166	1	-0.0066	1	0.5165	0.0407	0.7398	0.0097	-0.0144	0.2997
IL.17C	0.6847	0.2390	1.0939	0.0429	0.9402	0.1859	0.4092	0.7891	0.2555	1	-0.1536	1	0.6847	0.1285	1.0939	0.0215	-0.0029	1
IL.18R1	0.3180	0.8214	0.5002	0.3173	0.7309	0.0538	0.1822	1	0.4129	0.4027	0.2307	1	0.3180	0.4215	0.5002	0.1587	-0.0015	1
IL10	0.5726	0.6461	0.6750	0.6916	0.5248	1	0.1025	1	-0.0478	1	-0.1503	1	0.5726	0.3339	0.6750	0.3458	0.0055	1
IL18	0.8423	0.0031	0.5166	0.4672	1.0593	0.0051	-0.3257	0.6001	0.2169	1	0.5427	0.1609	0.8423	0.0024	0.5166	0.2336	-0.0023	1
IL6	0.3373	1	0.4472	0.9669	0.6656	0.3317	0.1099	1	0.3283	1	0.2184	1	0.3373	0.6214	0.4472	0.4834	0.0160	0.4652
IL7	0.0441	1	0.0066	1	-0.2120	1	-0.0376	1	-0.2562	0.7842	-0.2186	1	0.0441	1	0.0066	1	0.0049	1
IL8	0.3922	1	1.1601	0.1736	0.7983	0.9822	0.7678	0.1953	0.4061	1	-0.3617	1	0.3922	1	1.1601	0.0868	0.0248	0.5456
LAP.TGF.beta.1	-0.1408	1	-0.0613	1	0.0079	1	0.0795	1	0.1486	1	0.0691	1	-0.1408	1	-0.0613	1	0.0058	1
LIF.R	0.1300	1	0.2288	0.2870	0.4489	0.0020	0.0988	1	0.3190	0.0094	0.2202	0.1356	0.1300	0.5326	0.2288	0.1435	0.0049	0.6891
MCP.1	0.5195	0.1048	0.5627	0.2015	0.7253	0.0673	0.0432	1	0.2058	1	0.1626	1	0.5195	0.0590	0.5627	0.1008	0.0091	0.9700
MCP.2	0.4646	0.3233	0.1798	1	0.5897	0.3689	-0.2848	0.8798	0.1251	1	0.4099	0.5402	0.4646	0.1714	0.1798	1	0.0052	1
MCP.3	0.3662	0.3128	0.0319	1	0.1913	1	-0.3342	0.1841	-0.1749	1	0.1593	1	0.3662	0.1661	0.0319	1	0.0109	0.5163
MCP.4	-0.1049	1	-0.0854	1	-0.3524	1	0.0195	1	-0.2474	1	-0.2670	1	-0.1049	1	-0.0854	1	0.0289	0.0418
MMP.1	0.1499	1	-0.0625	1	0.3351	1	-0.2124	1	0.1852	1	0.3976	1	0.1499	1	-0.0625	1	0.0126	1
MMP.10	0.0649	1	0.4824	0.9434	0.4614	1	0.4175	0.4289	0.3966	1	-0.0209	1	0.0649	1	0.4824	0.4717	-0.0093	1
NT.3	0.1709	1	0.0069	1	0.1830	1	-0.1640	1	0.0120	1	0.1760	1	0.1709	0.9330	0.0069	1	0.0104	0.4351
OPG	0.1597	1	0.4766	0.0860	0.6192	0.0186	0.3169	0.0965	0.4595	0.0389	0.1426	1	0.1597	0.9626	0.4766	0.0430	0.0162	0.0547
OSM	0.1274	1	0.3934	1	0.1494	1	0.2660	1	0.0220	1	-0.2440	1	0.1274	1	0.3934	0.7853	0.0149	0.6855
PD.L1	0.2840	0.6261	0.4190	0.2854	0.8428	0.0014	0.1349	1	0.5588	0.0147	0.4238	0.0995	0.2840	0.3239	0.4190	0.1427	0.0078	0.8780
SCF	-0.1471	1	-0.4807	0.4305	-0.7611	0.0512	-0.3335	0.3899	-0.6140	0.0511	-0.2805	1	-0.1471	1	-0.4807	0.2152	-0.0051	1
SIRT2	0.0383	1	-0.0572	1	-0.7747	0.2162	-0.0955	1	-0.8130	0.0382	-0.7175	0.0730	0.0383	1	-0.0572	1	0.0093	1
SLAMF1	0.6988	0.0006	0.5336	0.0898	1.0676	0.0000	-0.1652	1	0.3688	0.3150	0.5340	0.0220	0.6988	0.0006	0.5336	0.0449	0.0001	1
ST1A1	0.3098	1	0.1039	1	-0.0571	1	-0.2059	1	-0.3669	1	-0.1610	1	0.3098	0.8502	0.1039	1	0.0227	0.1931
STAMBP	0.0880	1	0.0007	1	-0.6540	0.2024	-0.0873	1	-0.7420	0.0169	-0.6547	0.0374	0.0880	1	0.0007	1	0.0119	0.7038
TGF.alpha	0.0839	1	0.2131	0.5898	0.2909	0.2262	0.1292	0.8276	0.2070	0.3999	0.0778	1	0.0839	1	0.2131	0.2949	0.0107	0.0597
TNF	0.6380	0.0095	0.5907	0.0971	0.8567	0.0072	-0.0474	1	0.2186	1	0.2660	1	0.6380	0.0065	0.5907	0.0485	0.0020	1
TNFB	0.4310	0.1129	0.5945	0.0475	0.6247	0.0556	0.1635	1	0.1937	1	0.0301	1	0.4310	0.0632	0.5945	0.0238	-0.0039	1
TNFRSF9	0.7191	0.0020	0.5175	0.1986	0.8942	0.0039	-0.2015	1	0.1751	1	0.3767	0.3694	0.7191	0.0017	0.5175	0.0993	0.0044	1
TNFSF14	0.2851	0.9167	0.4125	0.5178	0.5002	0.3316	0.1273	1	0.2150	1	0.0877	1	0.2851	0.4691	0.4125	0.2589	0.0115	0.5189
TRAIL	0.3529	0.0223	0.2637	0.4349	0.6153	0.0007	-0.0892	1	0.2624	0.2454	0.3516	0.0273	0.3529	0.0141	0.2637	0.2175	-0.0015	1
TRANCE	0.0457	1	-0.5343	0.3977	-0.2964	1	-0.5800	0.0222	-0.3421	1	0.2379	1	0.0457	1	-0.5343	0.1989	-0.0209	0.1282
TWEAK	-0.1128	1	-0.0919	1	-0.1406	1	0.0209	1	-0.0279	1	-0.0487	1	-0.1128	1	-0.0919	1	-0.0004	1
uPA	0.2074	1	0.5059	0.0611	0.7728	0.0015	0.2985	0.1465	0.5654	0.0055	0.2669	0.5966	0.2074	0.6081	0.5059	0.0306	0.0041	1
VEGFA	0.2666	0.2656	0.3894	0.0943	0.5284	0.0139	0.1227	1	0.2618	0.3673	0.1391	1	0.2666	0.1421	0.3894	0.0471	0.0089	0.3404

Variable	HIV-CON		IDU-CON		DP-CON		IDU-HIV		DP-HIV		DP-IDU		HIV		IDU		Interaction	
	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Mean Estimate Difference	ANCOVA p-value	Coefficient Estimate	2-Way ANOVA p-value	Coefficient Estimate	2-Way ANOVA p-value	Coefficient Estimate	2-Way ANOVA p-value
Granulocytes	-0.0309	1	0.0123	1	0.0258	1	0.0432	1	0.0567	1	0.0135	1	-0.0309	1	0.0123	1	0.0023	0.7495
Neutrophils	0.0001	1	0.0484	1	0.0809	0.9788	0.0483	1	0.0808	0.6281	0.0325	1	0.0001	1	0.0484	1	0.0002	1
Eosinophils	0.0121	1	-0.0337	1	-0.0638	1	-0.0457	1	-0.0758	0.6816	-0.0301	1	0.0121	1	-0.0337	1	0.0001	1
Basophils	-0.0012	1	-0.0032	1	-0.0065	0.0618	-0.0021	1	-0.0053	0.0838	-0.0033	0.6613	-0.0012	1	-0.0032	0.5584	0.0000	1
Lymphocytes	0.0376	1	-0.0097	1	-0.0226	1	-0.0474	1	-0.0602	1	-0.0128	1	0.0376	1	-0.0097	1	-0.0027	0.5030
Total B Cells	-0.0063	1	-0.0188	1	-0.0036	1	-0.0124	1	0.0027	1	0.0152	1	-0.0063	1	-0.0188	1	-0.0011	0.7080
Naive B Cells	-0.0605	1	-0.1902	0.1483	-0.1026	1	-0.1297	0.2606	-0.0421	1	0.0876	1	-0.0605	1	-0.1902	0.0742	0.0011	1
Total Memory B Cells	0.0602	1	0.1877	0.1581	0.1014	1	0.1276	0.2792	0.0412	1	-0.0863	1	0.0602	1	0.1877	0.0791	-0.0012	1
Naive B Cells IgD (-/+)	-0.0564	1	-0.1867	0.1540	-0.1009	1	-0.1302	0.2416	-0.0445	1	0.0858	1	-0.0564	1	-0.1867	0.0770	0.0009	1
IgD- Memory B Cells	0.0719	0.4696	0.1440	0.0365	0.0846	0.6595	0.0720	0.3937	0.0127	1	-0.0594	0.9877	0.0719	0.2535	0.1440	0.0182	0.0000	1
Total Monocytes	-0.0389	1	-0.0088	1	-0.0056	1	0.0301	1	0.0333	1	0.0032	1	-0.0389	0.7320	-0.0088	1	0.0000	1
Classical Monocytes	-0.0083	1	0.0022	1	0.0210	1	0.0104	1	0.0293	1	0.0188	1	-0.0083	1	0.0022	1	-0.0027	0.1412
Transitional Monocytes	0.0101	1	0.0065	1	-0.0058	1	-0.0036	1	-0.0159	1	-0.0123	1	0.0101	1	0.0065	1	0.0006	0.8231
Nonclassical Monocytes	0.0114	1	-0.0009	1	-0.0051	1	-0.0123	1	-0.0164	1	-0.0041	1	0.0114	1	-0.0009	1	0.0011	0.5499
Total NK	-0.0040	1	0.0236	1	-0.0243	1	0.0276	0.5211	-0.0202	1	-0.0479	0.0499	-0.0040	1	0.0236	0.7838	0.0000	1
Late NKs	0.2683	0.0262	0.2166	0.4026	0.2128	0.4864	-0.0517	1	-0.0556	1	-0.0039	1	0.2683	0.0191	0.2166	0.2013	-0.0007	1
Early NKs	-0.2670	0.0271	-0.2153	0.4100	-0.2115	0.4942	0.0517	1	0.0554	1	0.0038	1	-0.2670	0.0196	-0.2153	0.2050	0.0008	1
Total T Cells	0.0476	0.8370	0.0158	1	0.0310	1	-0.0317	1	-0.0165	1	0.0152	1	0.0476	0.4377	0.0158	1	0.0012	1
Gamma Delta T Cells	-0.0132	1	-0.0027	1	-0.0277	1	0.0105	1	-0.0145	1	-0.0250	1	-0.0132	1	-0.0027	1	0.0007	0.9768
MAIT/NKT Cells	-0.0368	0.0213	-0.0081	1	-0.0092	1	0.0287	0.1130	0.0276	0.2941	-0.0011	1	-0.0368	0.0160	-0.0081	1	-0.0006	0.7246
CD3+ ab T cells	0.0050	1	0.0044	1	0.0253	1	-0.0006	1	0.0203	1	0.0210	1	0.0050	1	0.0044	1	-0.0007	1
CD4 ab T Cells	-0.2467	0.0000	-0.0534	1	-0.2232	0.0039	0.1933	0.0010	0.0235	1	-0.1698	0.0122	-0.2467	0.0000	-0.0534	1	-0.0009	1
Th1-like	0.0051	1	0.0204	1	-0.0067	1	0.0153	1	-0.0118	1	-0.0270	0.5136	0.0051	1	0.0204	0.8210	0.0008	0.5314
Th17-like	0.0116	1	0.0244	1	0.0264	1	0.0127	1	0.0148	1	0.0021	1	0.0116	1	0.0244	0.7650	-0.0003	1
Th2-like	0.0060	1	-0.0105	1	-0.0122	1	-0.0166	1	-0.0183	1	-0.0017	1	0.0060	1	-0.0105	1	0.0005	1
Treg	0.0058	1	0.0027	1	0.0170	0.2494	-0.0031	1	0.0112	0.7013	0.0143	0.2144	0.0058	1	0.0027	1	0.0002	1
CD4 Terminal Effectors	0.0506	0.1372	0.1203	0.0003	0.0751	0.0548	0.0697	0.0094	0.0245	1	-0.0452	0.3247	0.0506	0.0818	0.1203	0.0002	0.0019	0.1373
CD4 Effector Memory	-0.0267	1	0.0221	1	0.0282	1	0.0488	1	0.0549	1	0.0061	1	-0.0267	1	0.0221	1	0.0022	0.9362
CD4 Central Memory	0.0016	1	0.0786	0.2523	0.0193	1	0.0769	0.0595	0.0177	1	-0.0592	0.3986	0.0016	1	0.0786	0.1261	-0.0026	0.1311
CD4 Naive	-0.0180	1	-0.1225	0.4054	-0.1028	0.8209	-0.1044	0.2500	-0.0847	0.9187	0.0197	1	-0.0180	1	-0.1225	0.2027	-0.0034	0.3774
Activated CD4 T cells	0.0246	0.3835	0.0082	1	0.0632	0.0015	-0.0164	1	0.0385	0.0555	0.0549	0.0012	0.0246	0.2098	0.0082	1	0.0002	1
CD8 ab T Cells	0.2691	0.0000	0.0365	1	0.2330	0.0001	-0.2326	0.0000	-0.0361	1	0.1965	0.0002	0.2691	0.0000	0.0365	1	-0.0001	1
CD8 Terminal Effector	0.0862	1	0.0484	1	0.1556	0.8013	-0.0378	1	0.0694	1	0.1072	1	0.0862	0.8607	0.0484	1	0.0023	1
CD8 Effector Memory	-0.0253	1	0.0300	1	0.0120	1	0.0554	1	0.0373	1	-0.0181	1	-0.0253	1	0.0300	1	0.0081	0.0211
CD8 Naive	-0.0623	1	-0.0804	1	-0.1633	0.8323	-0.0180	1	-0.1010	1	-0.0829	1	-0.0623	1	-0.0804	1	-0.0103	0.0145
Activated CD8+ T cells	0.0804	0.1888	0.0203	1	0.0859	0.4549	-0.0601	0.5531	0.0056	1	0.0657	0.5661	0.0804	0.1093	0.0203	1	0.0007	1
TEMRA CD8+ T cells	0.0586	1	0.0356	1	0.0540	1	-0.0230	1	-0.0046	1	0.0184	1	0.0586	1	0.0356	1	0.0031	0.9640

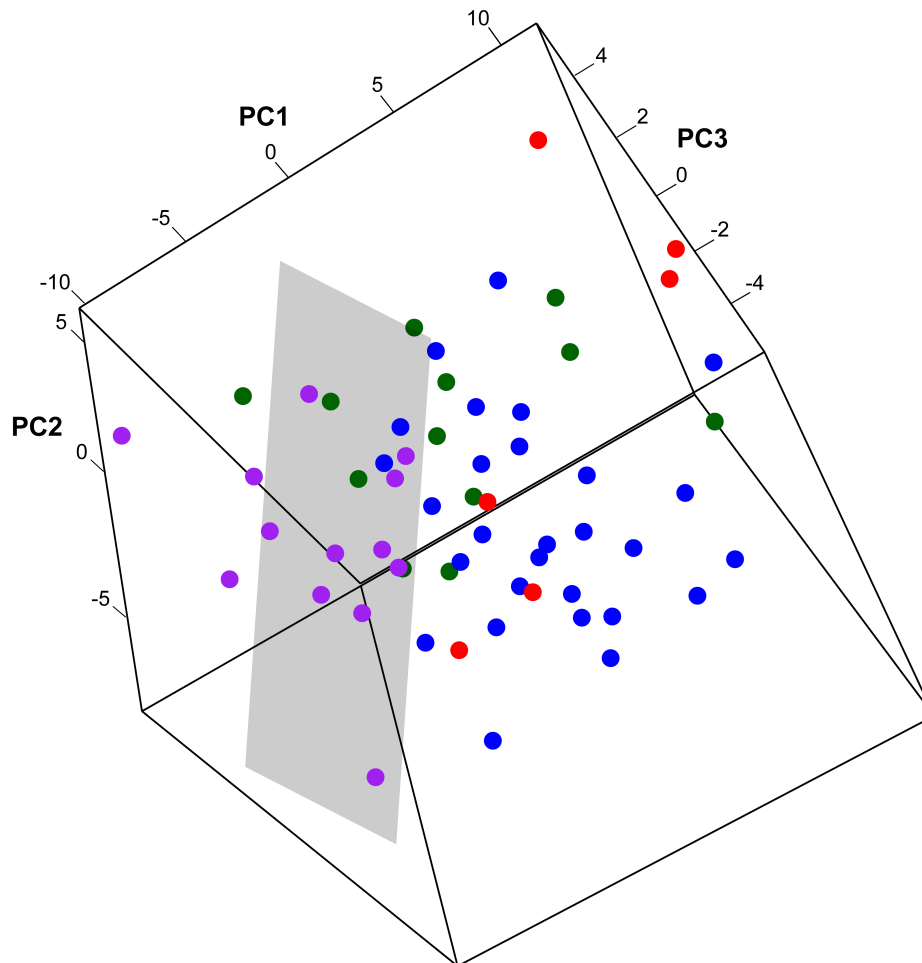
3 Supplementary Figures



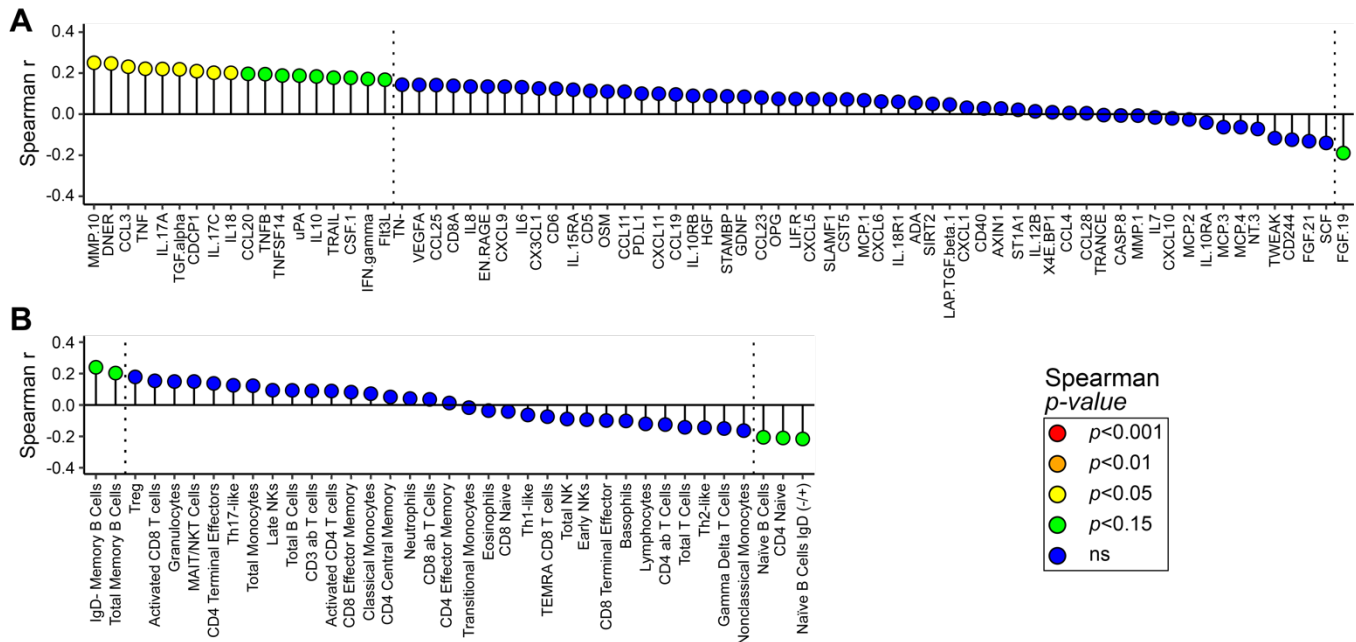
Supplementary Figure S1. Gating strategy for Maxpar Direct Immune Profiling Assay. The representative plots demonstrate the various gates applied to quantify the number of cells from each immune cell type, where the arrows designate the input population into each plot. Created with BioRender.com.



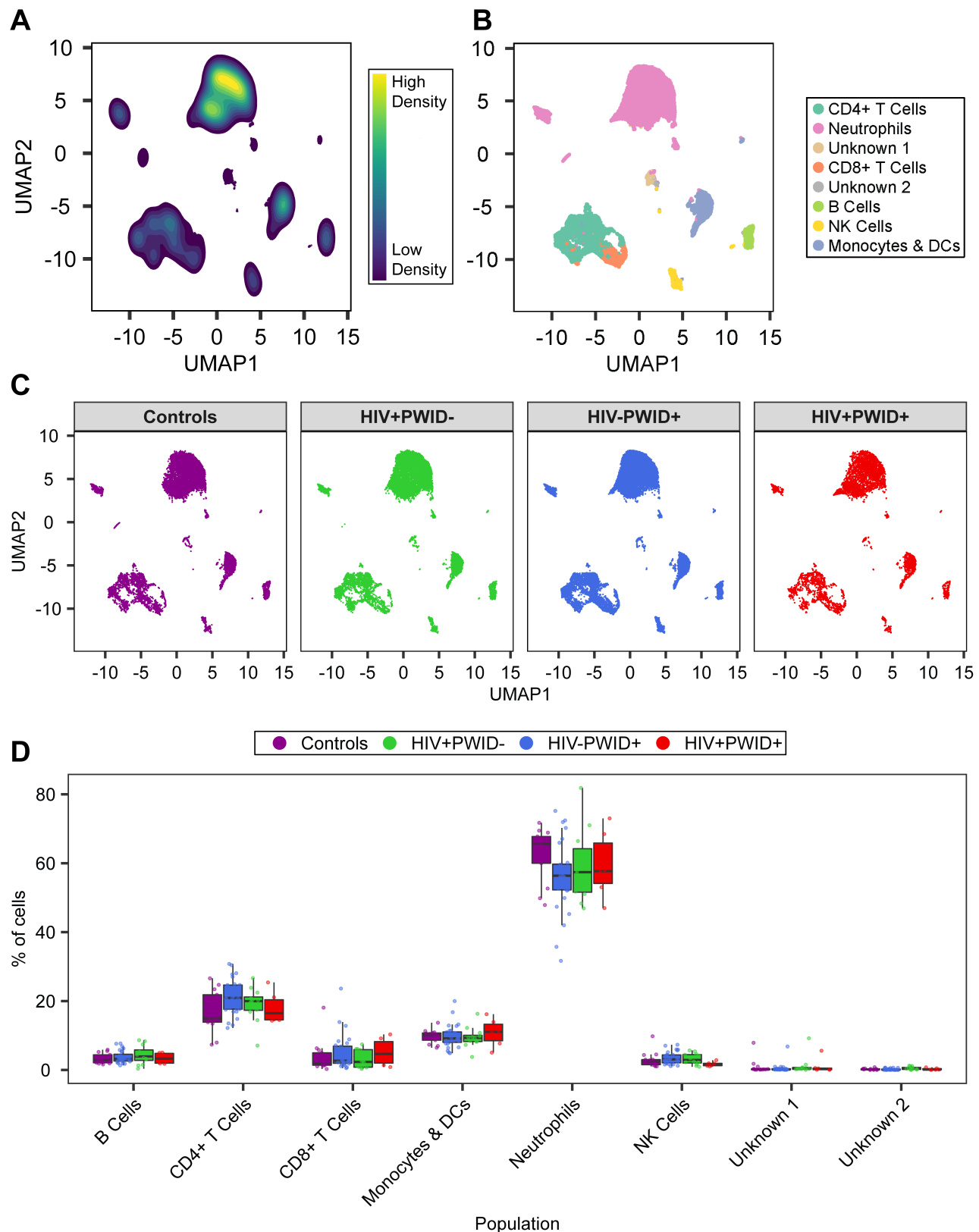
Supplementary Figure S2. Drug co-occurrence across the 97 participants. Frequencies of co-occurrence based on self-report of (A) non-injection drug use and (B) injection drug use in the last 12 months were calculated for each drug of interest.



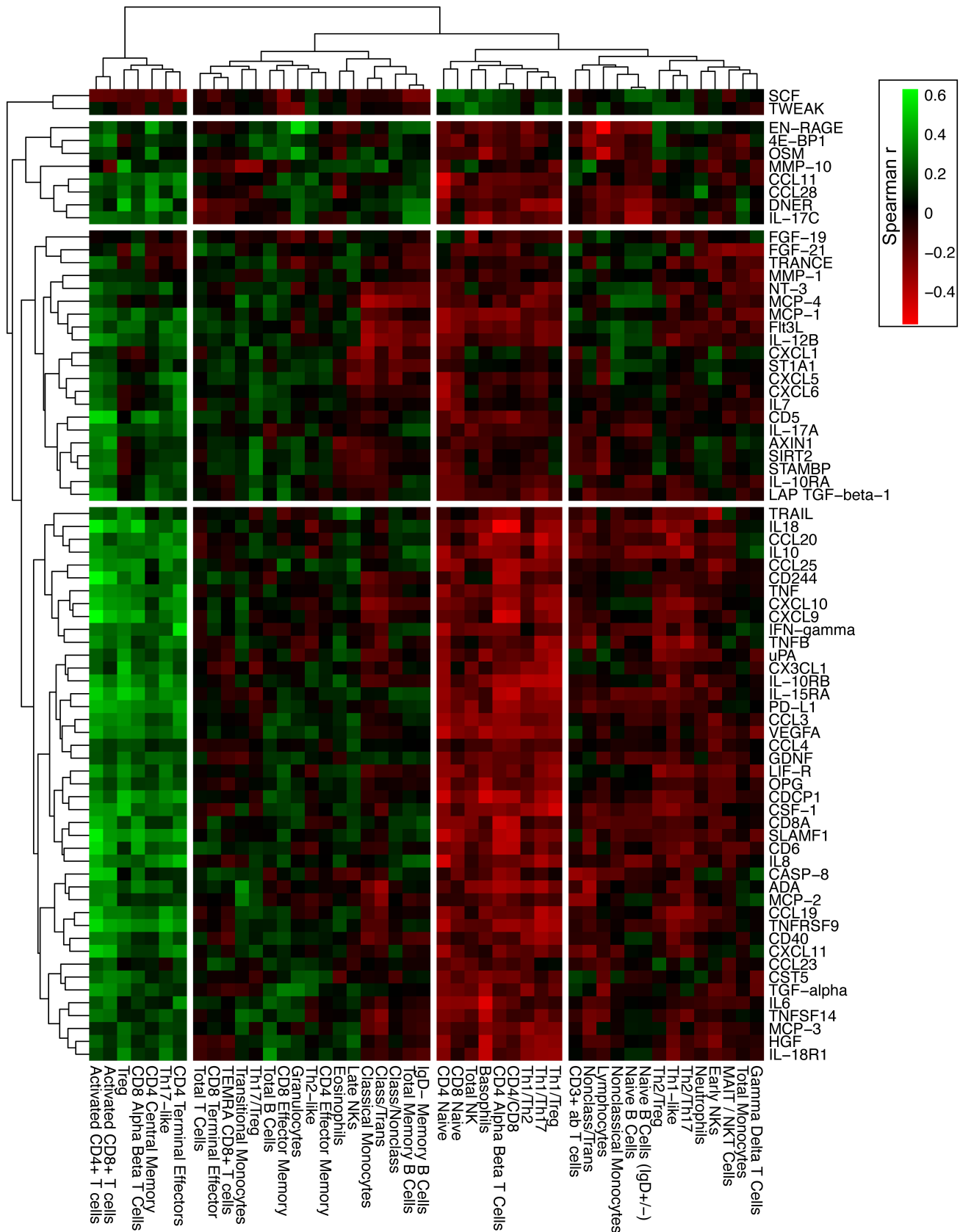
Supplementary Figure S3. 3D projected principal component analysis of inflammatory mediators and cellular immunophenotypes. With the combined inputs of Bridge normalized NPX values from Olink Target 96 Inflammation Panel and the percent of lineage parent population for each of 37 immune cell types, principal component analysis (PCA) was performed and projected in 3-dimensions. The input data was standardized and centered. The individuals are colored by group (HIV: HIV⁺/PWID⁻, IDU: HIV⁻/PWID⁺, DP: HIV⁺/PWID⁺, CON: HIV⁻/PWID⁻). A gray hyperplane was drawn to demonstrate the segregation of the control group from the other groups. Generated using the R package, rgl v1.0.1.



Supplementary Figure S4. Correlations of inflammatory mediators and cellular immunophenotypes with the degree of poly-substance use. Spearman correlations of the (A) bridge normalized NPX values for the 74 inflammatory mediators and (B) 37 immune cell types represented as the frequency of lineage parent were calculated after adjusting for age, homeless in the last year or now, male identity, married, employed, and some college experience. The y-axis represents the partial correlation coefficient, while the color of the point represents the p -value of the spearman correlation. Generated using the R package, ggplot2 v3.3.6.



Supplementary Figure S5. Clustering of mass cytometry data validated bivariate gating strategy. The immunoCluster R package was used to perform (A) uniform manifold approximation and projection (UMAP) data reduction and (B) self-organizing maps (SOM) with consensus clustering (k=8). The cluster identities were estimated based on cell-marker levels within the clusters when possible. The UMAP projections were (C) split into cohorts and (D) quantified as percent of live cells per sample. Generated using the ImmunoCluster program (<https://github.com/kordastilab/ImmunoCluster>).



Supplementary Figure S6. Correlations of inflammatory mediators with cellular immunophenotypes. The color of the cell represents the spearman correlation of the given inflammatory mediator and the ratio or frequency of the given cell type, as denoted by the legend. Generated using the R package, pheatmap v1.0.12.