Supplementary Methods

Study population
Participants from the NeuroAIDS Tissue Consortium (NNTC) included the Texas NeuroAIDS Research Center (Galveston, TX), National Neurological AIDS Bank (Los Angeles, CA), Manhattan HIV Brain Bank (New York, NY), and California NeuroAIDS Tissue Network (San Diego, CA). Participants from the HIV Neurobehavioral Research Center (HNRC) (San Diego, CA) included CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER). Participants from the Multicenter AIDS Cohort Study (MACS) were all enrolled at the Chicago site. Two HIV+ participants not meeting all selection criteria were included (baseline plasma viral load >1500 copies/mL but viral load <200 copies/mL at prior and subsequent visits). The sample (n=245) and group sizes (n=105 marijuana smokers, n=110 tobacco smokers) were sufficient to detect an effect size (difference in metabolite means) of 0.35 between these smoking groups or 0.50 between the smallest subgroup of marijuana or tobacco smokers (n=45) compared to non-smokers (n=88) at 80% power (α=0.05). For logistic regressions, the number of events (n=30) and proportions of subjects with events among marijuana and tobacco smokers were sufficient to detect univariate odds ratios >2.0 at 80% power (α=0.05).

Plasma metabolite profiling
Untargeted metabolomic profiling was performed by Metabolon (Durham, NC) combining three independent platforms: ultra-high performance liquid chromatography and tandem mass spectrometry (UHLC/MS2/MS) optimized for detection of acidic metabolites, UHLC/MS2/MS optimized for detection of basic metabolites, and gas chromatography/mass spectrometry (GC/MS) as previously described [1,2]. Plasma samples (100 uL) were extracted using the MicroLab STAR system as described. Briefly, protein was precipitated from plasma with methanol containing four standards to monitor extraction efficiency. The resulting supernatant was split into equal aliquots for analysis on the three platforms. Aliquots, dried under nitrogen, were subsequently reconstituted in 50 µL 0·1% formic acid in water (acidic conditions) or in 50 µL 6·5 mM ammonium bicarbonate in water, pH 8 (basic conditions) for the two UHPLC/MS/MS analyses or derivatized to a final volume of 50 µL for GC/MS analysis using equal parts bistrimethyl-silyl-trifluoroacetamide and solvent mixture acetonitrile:dichloromethane:cyclohexane (5:4:1) with 5% triethylamine at 60°C for one hour. Three types of controls were utilized: samples derived from pooled experimental samples served as technical replicates, extracted water samples served as blanks, and a cocktail of standards spiked into every analyzed sample allowed instrument performance monitoring. The UHLC/MS2/MS platform was based on a Waters ACQUITY UHPLC and Thermo-Finnigan LTQ mass spectrometer, which consisted of an electrospray ionization source and linear ion-trap mass analyzer. Derivatized samples for GC/MS were separated on 5% phenyldimethyl silicone columns, with helium as the carrier gas and a temperature ramp from 60°C to 340°C over a 16-minute period. Analysis was performed on a Thermo-Finnigan Trace DSQ fast-scanning single-quadrupole mass spectrometer operated at unit mass resolving power with electron impact ionization and a 50-750 atomic mass unit scan range. Compounds were identified by automated comparison of the ion features in the experimental samples to a reference library of over 4,000 chemical standard entries that included retention time, molecular weight (m/z), preferred adducts, and in-source fragments as well as associated MS spectra and curated by visual inspection for quality control using software developed at Metabolon. Missing values were imputed with the lower limit of detection (LOD) per metabolite.

Urine metabolite measurements
Urine biomarkers were analyzed at the Division of Laboratory Sciences of the National Center for Environmental Health at the Centers for disease control (CDC) [3,4]. Urine samples were assayed for 2 classes of biomarker compounds: tobacco alkaloids (7 nicotine metabolites and 2 minor tobacco alkaloids, ANBT and ANTT), and 24 metabolites of volatile organic compounds (VOCs) using ultra-high performance liquid chromatography with electrospray tandem mass spectrometry. LOD ranged from 0·4 to 15 ng/mL. Participants with measurements below these limits were assigned the value of the LOD divided by the square root of two Urine creatinine concentration was measured using a colorimetric method based on Jaffé rate reaction.

Statistical Analyses
All data preparation and analyses were performed in R (version 3.6.1). Cross-sectional analyses were performed using Welch's *t*-test (continuous variables) or Pearson's Chi-squared test (categorical variables); cross-sectional analyses of metabolite data were performed at study. Data were visualized using the *ComplexHeatmap* package, *ggpubr* with Welch's t-tests for box/dot plots, and *ggplot2*. Geometric means and 95% confidence intervals (CIs) were calculated with *DescTools* package. Intraclass correlation coefficients and 95% CIs were estimated with the *ICC* package using one-way ANOVA variance components. Mixed-effects models were fit using the *nlme* package. Variance inflation factors in multivariate logistic regression models (VIFs) were calculated using the *jtools* package and were <2·0 in all models, indicating no substantial multicollinearity between predictors.

References

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2. Chettimada S, Lorenz DR, Misra V, et al. Exosome markers associated with immune activation and oxidative stress in HIV patients on antiretroviral therapy. *Sci Rep* 2018; **8**(1): 7227.
3. Alwis KU, Blount BC, Britt AS, Patel D, Ashley DL. Simultaneous analysis of 28 urinary VOC metabolites using ultra high performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (UPLC-ESI/MSMS). *Anal Chim Acta* 2012; **750**: 152-60.
4. Wei B, Feng J, Rehmani IJ, et al. A high-throughput robotic sample preparation system and HPLC-MS/MS for measuring urinary anatabine, anabasine, nicotine and major nicotine metabolites. *Clin Chim Acta* 2014; **436**: 290-7.

Table S1. Intraclass correlation coefficients (95% confidence intervals) of nicotine, THC, PAH, and VOC plasma metabolites.

Metabolite	ICC (95% CI)	N	k
Metabolites of nicotine			
cotinine	0·896 (0·868-0·920)	165	2·83
hydroxycotinine	0·878 (0·845-0·906)	165	2·83
3-hydroxycotinine glucuronide	0·823 (0·777-0·862)	165	2·83
cotinine N-oxide	0·824 (0·778-0·862)	165	2·83
norcotinine	0·779 (0·710-0·835)	124	2·43
nornicotine	0·668 (0·573-0·747)	124	2·43
Metabolites of THC			
Δ9-trans-tetrahydrocannabinol (THC)	0·709 (0·641-0·768)	165	2·83
THC carboxylic acid	0·813 (0·765-0·854)	165	2·83
THC carboxylic acid glucuronide	0·837 (0·795-0·873)	165	2·83
Metabolites of PAHs			
2-naphthol sulfate	0·651 (0·574-0·720)	165	2·83
methylnaphthyl sulfate (1)	0·739 (0·677-0·794)	165	2·83
methylnaphthyl sulfate (2)	0·458 (0·334-0·573)	124	2·43
2-hydroxyfluorene sulfate	0·498 (0·404-0·586)	165	2·83
VOCs and other metabolites			
N-Acetyl-S-(3-hydroxypropyl)-L-cysteine (3HPMA)	0·622 (0·542-0·695)	165	2·83
o-cresol sulfate	0·668 (0·594-0·734)	165	2·83
3-acetylphenol sulfate	0·789 (0·735-0·834)	165	2·83
4-vinylphenol sulfate	0·442 (0·345-0·536)	165	2·83
catechol sulfate	0·800 (0·749-0·843)	165	2·83
quinate	0·735 (0·672-0·790)	165	2·83
2-ethylphenyl sulfate	0·869 (0·834-0·898)	165	2·83
4-ethylphenyl sulfate	0·839 (0·796-0·874)	165	2·83
3-hydroxy-2-methylpyridine sulfate	0·497 (0·339-0·634)	77	2·39
3-hydroxypyridine glucuronide	0·602 (0·463-0·718)	77	2·39
3-hydroxypyridine sulfate	0·663 (0·588-0·730)	165	2·83
1,2,3-benzenetriol sulfate (2)	0·482 (0·387-0·572)	165	2·83
4-vinylguaiacol sulfate	0·611 (0·529-0·685)	165	2·83
hydroquinone sulfate	0·533 (0·442-0·617)	165	2·83
isoeugenol sulfate	0·527 (0·437-0·613)	165	2·83

Within-subject ICCs for participants with ≥2 plasma metabolite measurements estimated using the variance components from a one-way ANOVA with the R *ICC* package. ICCs ≥0·75 considered excellent, 0·60-0·74, good, 0·40-0·59, fair, <0·40, poor. N denotes number of individuals, k, mean number of values per individual. Abbreviations: ICC, intraclass correlation coefficient, PAH, polycyclic aromatic hydrocarbons, VOC, volatile organic compounds.

Table S2. Intraclass correlations (95% confidence intervals) of nicotine-related and VOC urine metabolites·

Metabolite	Abbreviation	ICC (95% CI)	N	k
Nicotine and tobacco alkaloids (ng/mg creatinine)				
Cotinine	COTT	0·857 (0·774-0·915)	42	2·85
Hydroxycotinine	HCTT	0·861 (0·780-0·918)	42	2·85
Cotinine-n-oxide	COXT	0·852 (0·766-0·912)	42	2·85
Nicotine	NICT	0·772 (0·652-0·861)	42	2·85
Nicotine-1'N-oxide	NOXT	0·804 (0·697-0·882)	42	2·85
Nornicotine	NNCT	0·783 (0·668-0·869)	42	2·85
Anabasine	ANBT	0·742 (0·610-0·841)	42	2·85
Anatabine	ANTT	0·756 (0·630-0·851)	42	2·85
1-(3-Pyridyl)-1-butanol-4-carboxylic acid	HPBT	0·858 (0·776-0·916)	42	2·85
VOCs				
2-Methylhippuric acid	2MHA	0·591 (0·418-0·737)	42	2·85
3-Methylhippuric acid + 4-Methylhippuric acid	34MH	0·522 (0·337-0·686)	42	2·85
N-Acetyl-S-(2-carbamoylethyl)-L-cysteine	AAMA	0·689 (0·541-0·806)	42	2·85
N-Acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine	GAMA	0·567 (0·389-0·719)	42	2·85
N-Acetyl-S-(1-cyano-2-hydroxyethyl)-L-cysteine	CYHA	0·725 (0·589-0·831)	42	2·85
N-Acetyl-S-(2-cyanoethyl)-L-cysteine	CYMA	0·826 (0·728-0·896)	42	2·85
N-Acetyl-S-(2-carboxyethyl)-L-cysteine	CEMA	0·595 (0·423-0·740)	42	2·85
N-Acetyl-S-(3-hydroxypropyl)-L-cysteine	3HPMA	0·644 (0·484-0·775)	42	2·85
N-Acetyl-S-(benzyl)-L-cysteine	BMA	0·276 (0·078-0·483)	42	2·85
N-Acetyl-S-(n-propyl)-L-cysteine	BPMA	0·316 (0·118-0·519)	42	2·85
Mandelic acid	MADA	0·540 (0·357-0·699)	42	2·85
Phenylglyoxylic acid	PHGA	0·563 (0·385-0·717)	42	2·85
N-Acetyl-S-(phenyl)-L-cysteine	PMA	0·244 (0·048-0·454)	42	2·85
N-Acetyl-S- (2-hydroxypropyl)-L-cysteine	HPM2	0·681 (0·531-0·801)	42	2·85
N-Acetyl-S-(phenyl-2-hydroxyethyl)-L-cysteine	PHEM	0·406 (0·210-0·595)	42	2·85
trans, trans-Muconic acid	MUCA	0·232 (0·037-0·444)	42	2·85
N-Acetyl-S-(N-methylcarbamoyl)-L-cysteine	AMCA	0·782 (0·666-0·868)	42	2·85
N-Acetyl-S-(2-hydroxyethyl)-L-cysteine	HEMA	0·665 (0·510-0·790)	42	2·85
N-Acetyl-S-(3,4-dihydroxybutyl)-L-cysteine	DHBM	0·388 (0·191-0·580)	42	2·85
N-Acetyl-S-(4-hydroxy-2-buten-1-yl)-L-cysteine	MHB3	0·776 (0·658-0·864)	42	2·85
N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine	HPMM	0·704 (0·560-0·816)	42	2·85
N-Acetyl-S-(4-hydroxy-2-methyl-2-buten-1-yl)-L-cys	IPM3	0·749 (0·621-0·846)	42	2·85
2-Thioxothiazolidine-4-carboxylic acid	TTCA	0·210 (0·016-0·423)	42	2·85
2-Aminothiazoline-4-carboxylic acid	ATCA	0·681 (0·530-0·800)	42	2·85

Within-subject ICCs for participants with ≥2 urine metabolite measurements estimated using the variance components from a one-way ANOVA with the R *ICC* package. ICCs ≥0·75 considered excellent, 0·60-0·74, good, 0·40-0·59, fair, <0·40, poor. N denotes number of individuals, k, mean number of values per individual. Abbreviations: ICC, intraclass correlation coefficient, PAH, polycyclic aromatic hydrocarbons, VOC, volatile organic compounds.

Table S3. Association between plasma metabolites, marijuana, and tobacco smoking in multivariable linear mixed-effects models.

	Model 1: main effects of marijuana and tobacco smoking status and their interaction term (reference: non-smoker)						Model 2: full factorial of marijuana and tobacco smoking status (reference: non-smoker)					
	MJ		TS		MJ X TS		MJ+ TS-		MJ- TS+		MJ+ TS+	
Metabolite	**Estimate**	***p* value**	**Estimate**	***p* value**	**Estimate**	***p* value**	**Estimate**	***p* value**	**Estimate**	***p* value**	**Estimate**	***p* value**
Metabolites of PAHs												
2-naphthol sulfate	0·82	0·0016	2·72	<0·0001	-0·80	0·012	0·82	0·0020	2·72	<0·0001	2·74	<0·0001
methylnaphthyl sulfate (1)	0·25	0·091	1·50	<0·0001								
methylnaphthyl sulfate (2)	0·84	<0·0001	3·13	<0·0001	-0·60	0·040	0·84	<0·001	3·13	<0·0001	3·37	<0·0001
2-hydroxyfluorene sulfate	0·47	<0·001	1·58	<0·0001								
VOCs and other metabolites												
N-Acetyl-S-(3-hydroxypropyl)-L-cysteine (3HPMA)	-0·10	0·36	0·99	<0·0001								
o-cresol sulfate	0·60	0·0015	2·18	<0·0001								
3-acetylphenol sulfate	0·22	0·37	0·95	<0·001								
4-vinylphenol sulfate	0·49	0·0036	1·03	<0·0001								
catechol sulfate	0·39	0·021	0·37	0·046								
quinate	0·31	0·31	0·80	0·015								
2-ethylphenyl sulfate	0·44	0·0028	2·34	<0·0001								
4-ethylphenyl sulfate	0·41	0·025	0·90	<0·0001								
3-hydroxy-2-methylpyridinesulfate	-0·19	0·66	0·69	0·075								
3-hydroxypyridine glucuronide	-0·16	0·63	0·37	0·22								
3-hydroxypyridine sulfate	0·30	0·29	1·44	<0·0001								
1,2,3-benzenetriol sulfate (2)	0·47	0·060	0·50	0·053								
4-vinylguaiacol sulfate	0·57	0·014	1·51	<0·0001								
hydroquinone sulfate	-0·13	0·44	0·50	0·0048								
isoeugenol sulfate	-0·14	0·44	1·44	<0·0001								

Models were fit for each indicated $\log_2$-transformed metabolite (dependent variables). Interactions between marijuana and tobacco smoking as separate binary variables were tested for each model and included where significant (left columns; $p<0·05$). A second model using the full factorial of marijuana and tobacco smoking status was fit for metabolites with significant MJ X TS interactions. All models were adjusted for age, HIV status, and renal function. Abbreviations: MJ, marijuana smoking, TS, tobacco smoking, PAHs, polycyclic aromatic hydrocarbons, VOCs, volatile organic compounds.

Table S4. Associations between urine VOC metabolites, marijuana, and tobacco smoking in multivariable linear mixed-effects models.

	Model 1: main effects of marijuana and tobacco smoking status and their interaction term (reference: non-smoker)						Model 2: full factorial of marijuana and tobacco smoking status (reference: non-smoker)					
Metabolite	**MJ**		**TS**		**MJ X TS**		**MJ+ TS-**		**MJ- TS+**		**MJ+ TS+**	
Abbreviation	**Estimate**	***p* value**	**Estimate**	***p* value**	**Estimate**	***p* value**	**Estimate**	***p* value**	**Estimate**	***p* value**	**Estimate**	***p* value**
2MHA	0·29	0·35	1·27	<0·001								
34MH	0·12	0·57	1·41	<0·0001								
AAMA	0·58	0·0023	0·84	<0·0001								
GAMA	0·39	0·038	0·52	0·010								
CYHA	1·50	0·0010	3·42	<0·0001	-1·40	0·017	1·39	0·0030	3·55	<0·0001	3·22	<0·0001
CYMA	2·93	<0·0001	5·41	<0·0001	-2·42	<0·001	2·54	<0·0001	5·85	<0·0001	5·59	<0·0001
CEMA	-0·03	0·88	1·15	<0·0001								
3HPMA	-0·06	0·79	1·35	<0·0001								
BMA	-0·11	0·70	-0·39	0·21								
BPMA	-0·09	0·81	-0·59	0·16								
MADA	0·37	0·089	0·81	<0·001								
PHGA	0·11	0·55	0·73	<0·001								
PMA	0·24	0·24	0·34	0·11								
HPM2	0·12	0·59	1·08	<0·0001								
PHEM	-0·04	0·87	0·70	0·0084								
MUCA	-0·12	0·66	1·07	<0·001								
AMCA	0·08	0·69	1·09	<0·0001								
HEMA	-0·31	0·28	0·48	0·12								
DHBM	-0·07	0·63	0·43	0·0038								
MHB3	0·30	0·21	2·04	<0·0001								
HPMM	-0·16	0·46	1·62	<0·0001								
IPM3	-0·12	0·68	2·35	<0·0001								
TTCA	0·32	0·19	-0·08	0·75								
ATCA	0·25	0·43	-0·56	0·11								

Models were fit for each indicated log2-transformed metabolite (dependent variable) for 89 participants with available urine metabolite data. Interactions between marijuana and tobacco smoking as separate binary variables were tested for each model and included where significant (left columns; p<0·05 A second model using the full factorial of marijuana and tobacco smoking status was fit for metabolites with significant MJ X TS interactions. All models were adjusted for age and HIV status. Refer to Table 3 for metabolite names. Abbreviations: MJ, marijuana smoking, TS, tobacco smoking, PAHs, polycyclic aromatic hydrocarbons, VOCs, volatile organic compounds.

Table S5. Association between plasma 3HPMA concentrations, tobacco smoking, and cardiovascular events among HIV positive participants.

	Unadjusted Models		Multivariable Model 1		Multivariable Model 2		Multivariable Model 3	
Predictor	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Tobacco smoking	1·87 (0·78-4·44)	0·16	1·81 (0·73-4·46)	0·20	1·09 (0·43-3·08)	0·78	1·15 (0·43-3·09)	0·78
Traditional CV risk factors (2-3 vs. 0-1)[a]	3·34 (1·41-7·94)	0·0061	3·28 (1·30-8·26)	0·012	3·82 (1·48-9·82)	0·0055	3·79 (1·45-9·88)	0·0064
3HPMA concentration (top vs. middle and lowest tertiles, scaled intensity)	2·81 (1·19-6·60)	0·018	–	–	3·03 (1·22-8·19)	0·029	–	–
3HPMA concentration (per 2-fold increase, scaled intensity)	1·53 (1·16-6·60)	0·0028	–	–	–	–	1·57 (1·15-2·15)	0·0044

Models were fit using logistic regression for 26 cardiovascular events among 183 HIV positive participants with plasma HPMA measurements. Events occurred within 5 years (median 1·08 years) prior to endpoint. Multivariable models also included terms for age. Cardiovascular events included myocardial infarction, coronary artery disease, cardiac stents, stroke, and atherosclerosis. Abbreviations: CV, cardiovascular, 3HPMA, N-Acetyl-S-(3-hydroxypropyl)-L-cysteine.

a - Number of traditional cardiovascular disease risk factors (hypertension, hyperlipidemia, diabetes risk factors - see Methods).

Table S6. Association between plasma o-cresol sulfate and methylnaphthyl sulfate (2) concentrations, tobacco smoking, and cardiovascular events.

	Unadjusted Models		Multivariable Model 1		Multivariable Model 2		Multivariable Model 3		Multivariable Model 4		Multivariable Model 5	
Predictor	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Tobacco smoking	2·28 (1·04-5·04)	0·0408	2·04 (0·87-4·80)	0·10	1·45 (0·55-3·80)	0·45	1·09 (0·40-3·00)	0·86	1·69 (0·54-5·31)	0·37	1·73 (0·51-5·84)	0·38
Traditional CV risk factors (2-3 vs. 0-1)[a]	3·70 (1·66-8·19)	0·0013	3·29 (1·43-7·58)	0·0052	3·36 (1·45-7·82)	0·0048	3·60 (1·51-8·54)	0·0039	3·27 (1·41-7·54)	0·0056	3·20 (1·42-7·55)	0·0055
o-cresol sulfate concentration (top vs. middle and lowest tertiles, scaled intensity)	2·53 (1·17-5·49)	0·019	–	–	2·16 (0·85-5·48)	0·11	–	–	–	–	–	–
o-cresol sulfate concentration (per 2-fold increase, scaled intensity)	1·31 (1·09-1·59)	0·0044	–	–	–	–	1·30 (1·04-1·64)	0·024	–	–	–	–
Methylnaphthyl sulfate (2) concentration (top vs. middle and lowest tertiles, scaled intensity)	2·11 (0·98-4·56)	0·057	–	–	–	–	–	–	1·32 (0·44-4·00)	0·62	–	–
Methylnaphthyl sulfate (2) concentration (per 2-fold increase, scaled intensity)	1·20 (0·99-1·40)	0·061	–	–	–	–	–	–	–	–	1·05 (0·80-1·38)	0·071

Models were fit using logistic regression for 30 cardiovascular events among 240 participants with plasma metabolite measurements. Events occurred within 5 years (median 1·08 years) prior to endpoint. Multivariable models also included terms for age and HIV status. Cardiovascular events included myocardial infarction, coronary artery disease, cardiac stents, stroke, and atherosclerosis. Abbreviations: CV, cardiovascular.

a - Number of traditional cardiovascular disease risk factors (hypertension, hyperlipidemia, diabetes risk factors - see Methods).

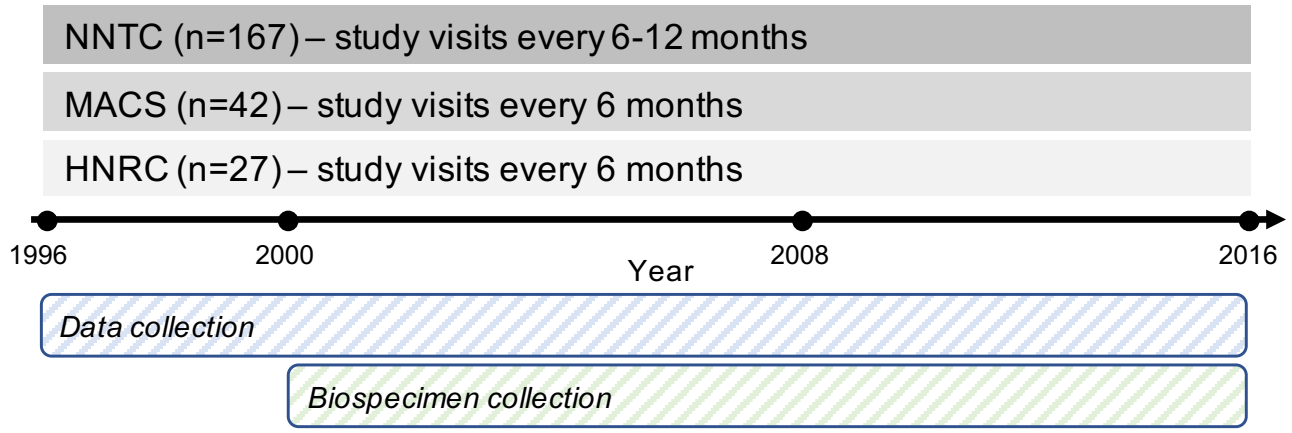

Figure S1. Timeline of study data and specimen collection from included U.S. HIV cohort studies. Schematic illustrating frequency of study visits and proportions of study participants enrolled in the National NeuroAIDS Tissue Consortium (NNTC, n=167), Chicago component of the Multicenter AIDS Cohort Study (MACS, n=42), and HIV Neurobehavioral Research Center (HNRC, n=27). Samples from nine additional HIV- controls were obtained from Bioreclamation IVT (Westbury, NY). Biospecimen collection included blood and urine; data collection included substance use, behavioral characteristics, medical conditions, medication use, and physical examinations (see Methods). All blood and urine samples used in this study were collected between 2000-2016

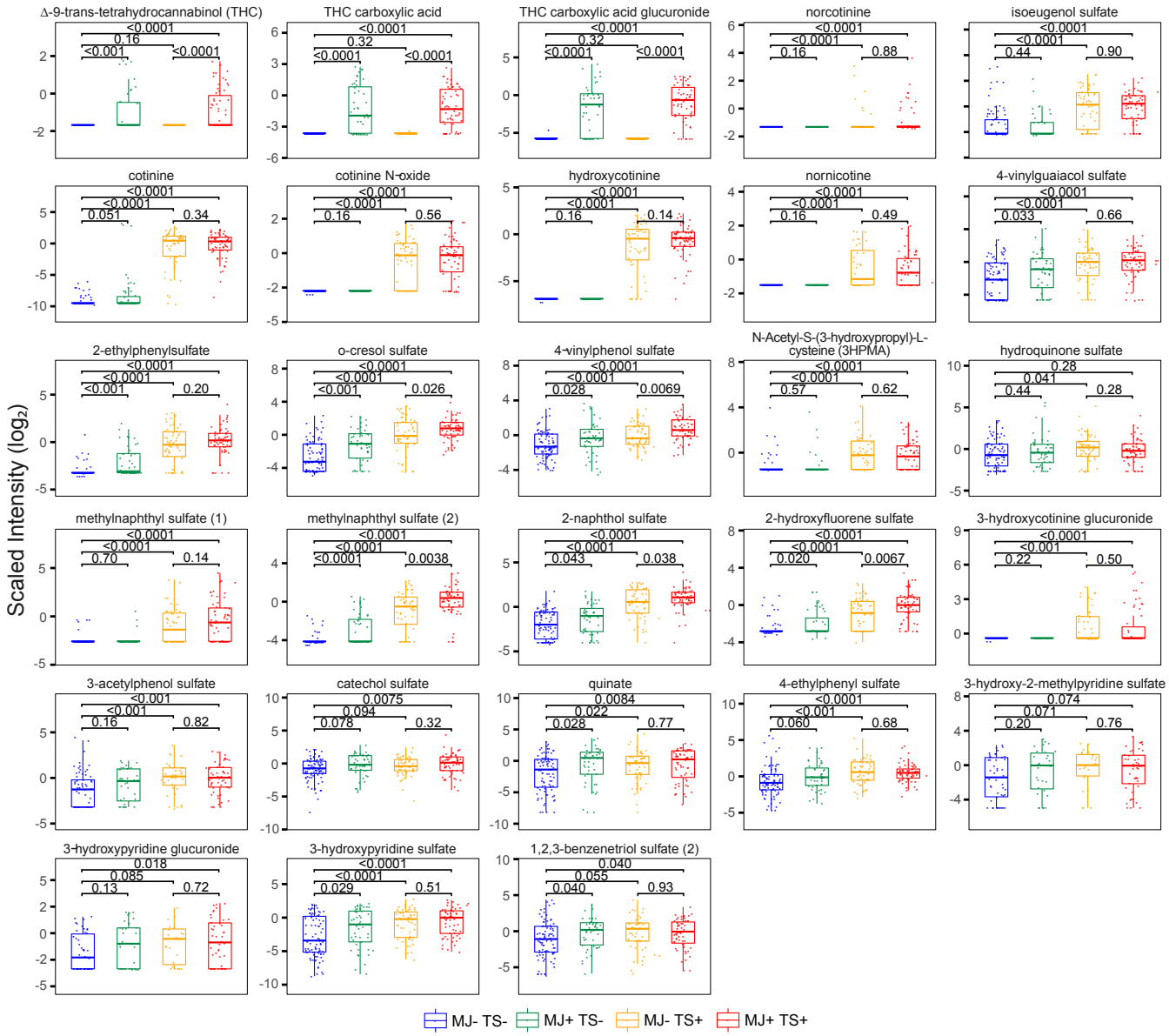

Figure S2. Plasma biomarkers of exposure by marijuana and tobacco smoking. Box plots of the complete set of analyzed plasma metabolites at study endpoint. Horizontal bars denote medians, boxes span IQRs, whiskers extend to 1·5 X IQR, dots denote individual participant values. MJ-TS- denotes non-smokers; MJ+TS-, marijuana-only smokers; MJ-TS+, tobacco-only smokers; MJ+TS+, dual marijuana-tobacco smokers.

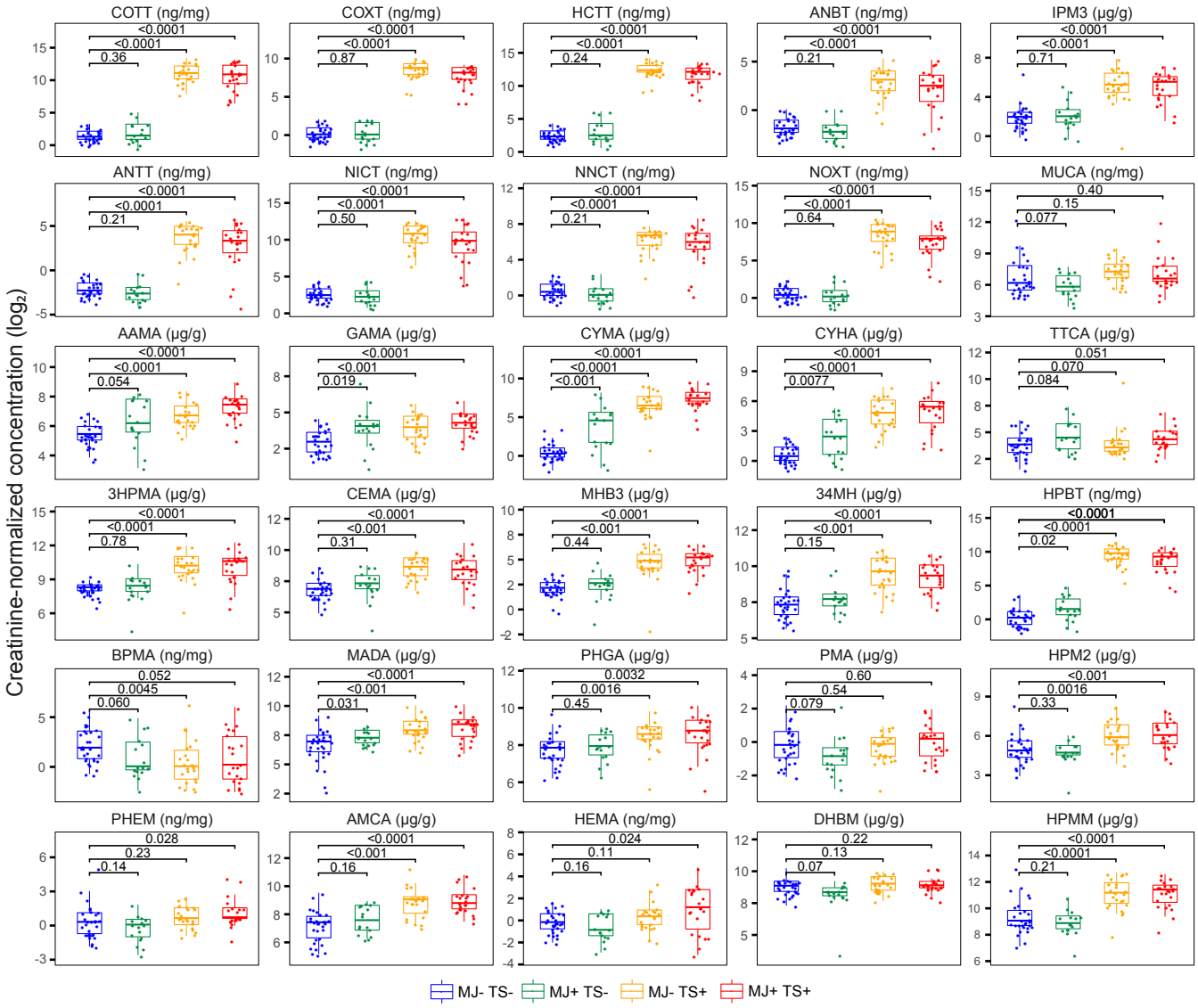

Figure S3. Urine biomarkers of exposure by marijuana and tobacco smoking. Box plots of the complete set of analyzed urine metabolite biomarkers at study endpoint. Horizontal bars denote medians, boxes span IQRs, whiskers extend to 1·5 X IQR, dots denote individual participant values. MJ-TS- denotes non-smokers; MJ+TS-, marijuana-only smokers; MJ-TS+, tobacco-only smokers; MJ+TS+, dual marijuana-tobacco smokers. Full names of metabolites corresponding to each abbreviation are shown in Table 3.

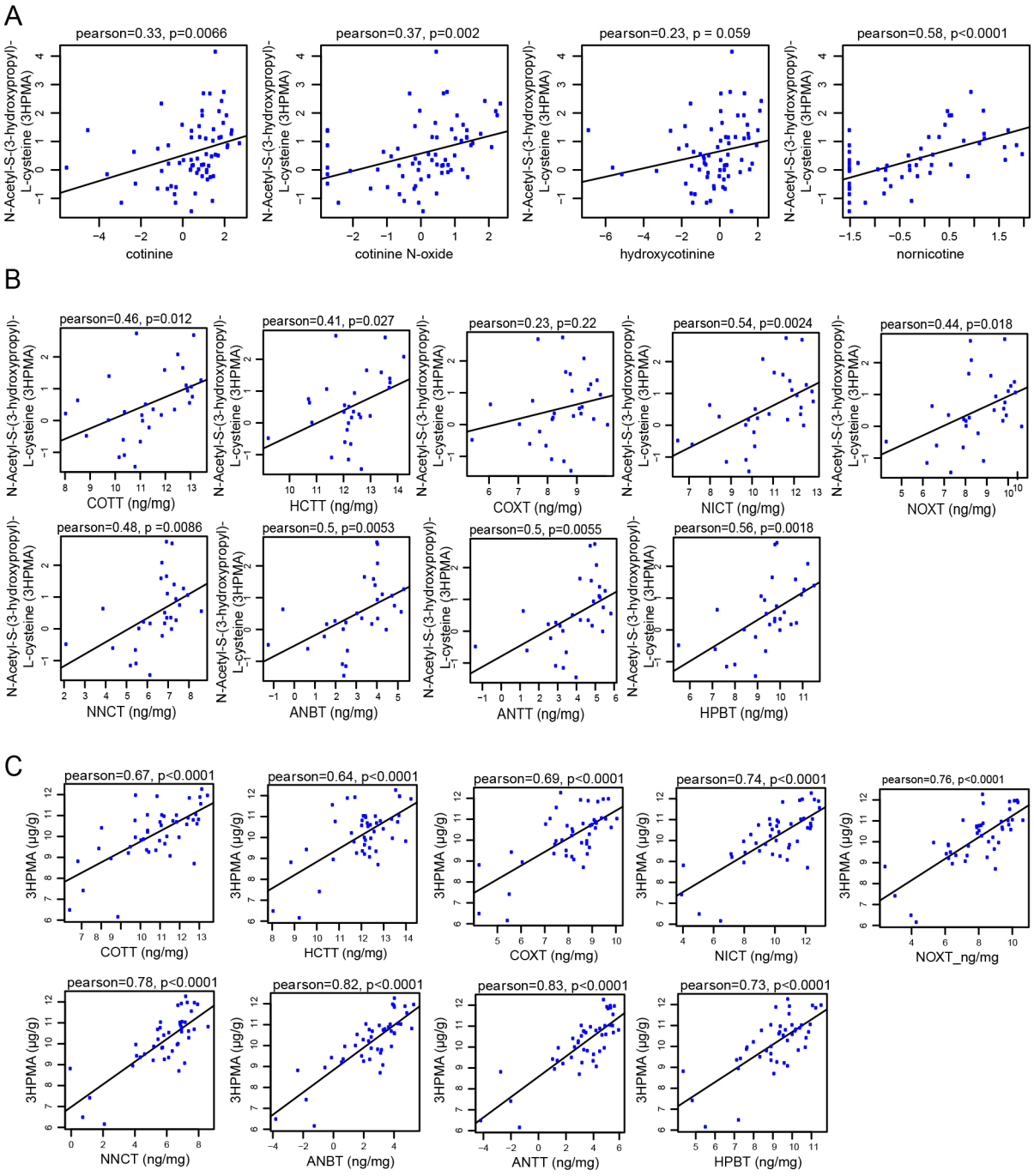

Figure S4. Correlations between plasma and urine nicotine and tobacco alkaloid metabolites and acrolein metabolite HPMA (S-(3-hydroxypropyl) mercapturic acid) among tobacco smokers. Pearson's correlation analysis for (A) plasma HPMA vs. plasma nicotine metabolites (n=68 tobacco smokers), (B), plasma HPMA vs. urine nicotine metabolites (n=29 tobacco smokers), (C) urine HPMA vs. urine nicotine metabolites (n=45 tobacco smokers). Dots denote metabolite levels from individual participants at study endpoint, lines denote Pearson's correlation coefficient. Both tobacco-only smokers (MJ-TS+) and dual marijuana-tobacco smokers (MJ+TS+) were included.

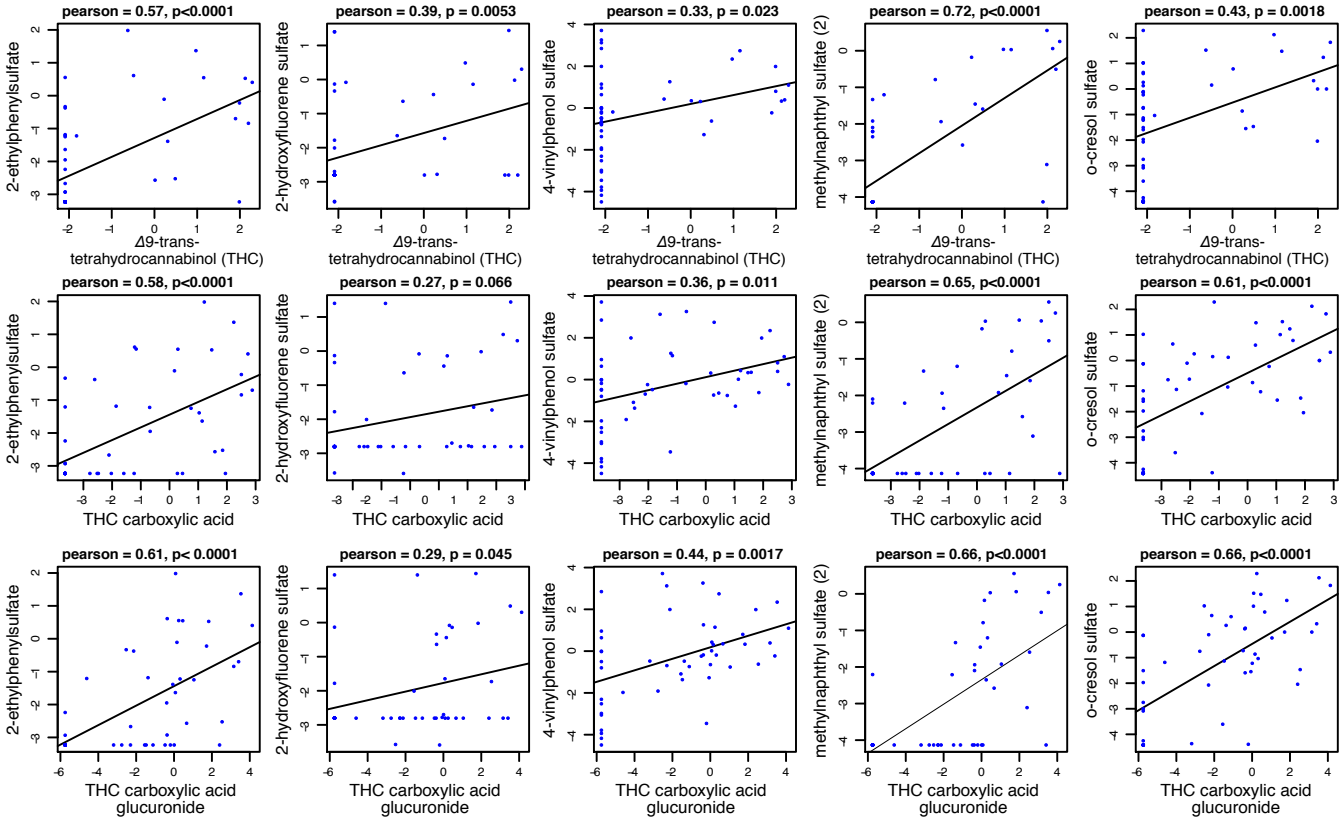

Figure S5. Correlations between plasma metabolites of THC and selected plasma metabolites among marijuana smokers. Pearson's correlation analysis for plasma metabolites of THC and selected plasma metabolites for n=44 marijuana-only smokers (MJ+TS-). Dots denote metabolite levels from individual participants at study endpoint, lines denote Pearson's correlation coefficient.

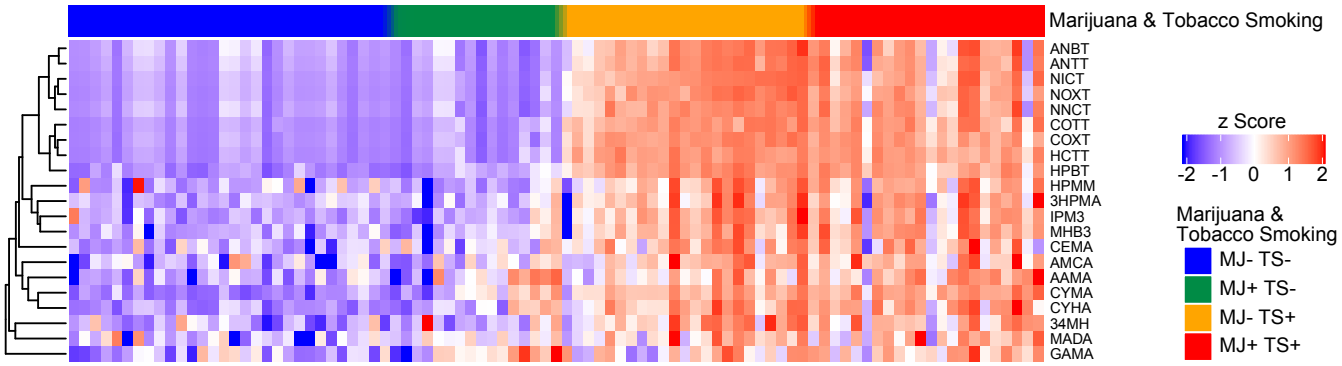

Figure S6. Heatmap of urine metabolites by marijuana and tobacco smoking. Metabolite intensities (rows) were standardized by *z*-scoring and clustered hierarchically. Individual participants (columns) were ordered by increasing THC or cotinine values within smoking groups (colored bar, top). MJ-TS- denotes non-smokers; MJ+TS-, marijuana-only smokers; MJ-TS+, tobacco-only smokers; MJ+TS+, dual marijuana-tobacco smokers. Full names of urine metabolites corresponding to each abbreviation are shown in Table 3.

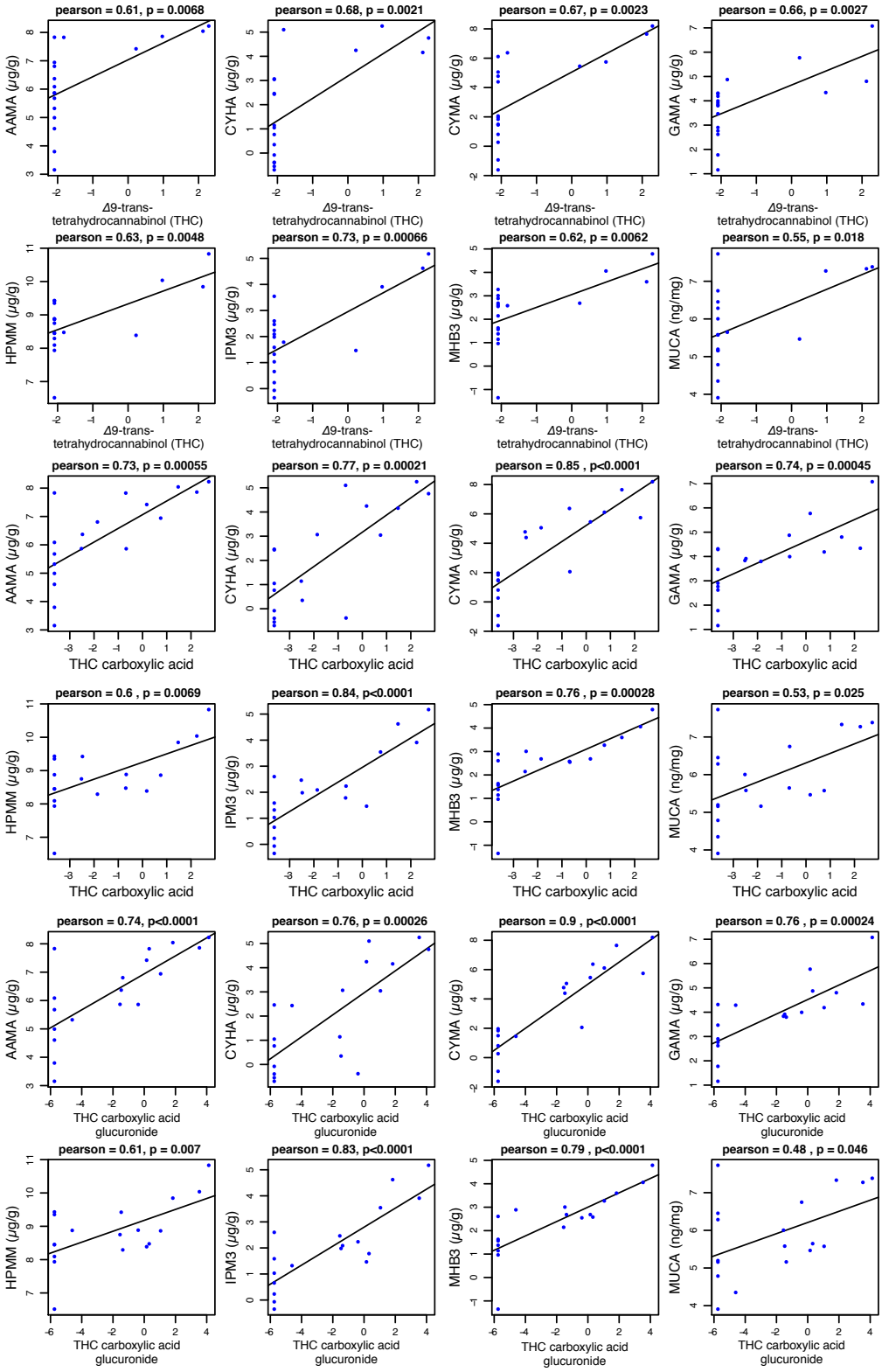

Figure S7. Correlations between plasma THC metabolites and selected urine metabolites among marijuana smokers. Pearson's correlation analysis for plasma metabolites of THC and selected plasma metabolites for n=18 marijuana-only smokers (MJ+TS-). Dots denote metabolite levels from individual participants at study endpoint, lines denote Pearson's correlation coefficient.