Title: Alterations of brain metabolites in adults with HIV: a systematic meta-analysis of MRS studies

Running Title**:** Metabolite alterations in HIV: a meta-analysis

Supplementary Online Content

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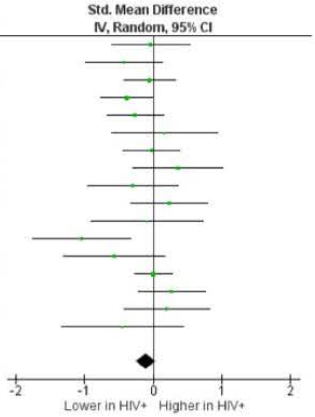
A

Basal Ganglia

NAA

Study or Subgroup	HIV+ Mean	HIV+ SD	HIV+ Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bairwa 2016	7.29	0.74	20	7.31	0.47	30	5.3%	-0.03 [-0.60, 0.53]
Bladowska 2013	1.52	0.18	41	1.59	0.1	18	5.3%	-0.43 [-0.99, 0.13]
Chang 2004	1.41	0.19	100	1.42	0.15	37	9.5%	-0.06 [-0.43, 0.32]
Cysique-BL 2018	4.33	0.47	84	4.5	0.37	42	9.6%	-0.38 [-0.76, -0.01]
Cysique-FU 2018	4.3	0.48	73	4.43	0.54	35	8.6%	-0.26 [-0.66, 0.15]
Ernst 2000	9.1	0.71	14	8.97	0.85	12	3.1%	0.16 [-0.61, 0.93]
Ernst 2010	7.47	0.84	45	7.49	0.81	46	8.4%	-0.02 [-0.43, 0.39]
Kallianpur 2013	1.32	0.14	35	1.27	0.11	12	4.1%	0.37 [-0.29, 1.03]
Koltowska 2010	1.53	0.2	25	1.59	0.2	14	4.1%	-0.29 [-0.95, 0.36]
Lee 2003	1.45	0.24	38	1.4	0.12	18	5.3%	0.24 [-0.33, 0.80]
Pulliam 2011	5.65	0.88	30	5.73	0.7	7	2.8%	-0.09 [-0.91, 0.73]
Roc 2007	1.21	0.09	45	1.33	0.19	10	3.6%	-1.04 [-1.76, -0.33]
Sailasuta 2012	1	0.14	26	1.08	0.13	10	3.3%	-0.57 [-1.31, 0.17]
Taylor 2007	7.16	1.08	106	7.15	0.95	99	13.6%	0.01 [-0.26, 0.28]
Valcour 2015	9.99	1.75	42	9.55	1.34	27	6.7%	0.27 [-0.21, 0.76]
VonGiesen 2001	1.51	0.14	32	1.48	0.17	14	4.4%	0.20 [-0.43, 0.83]
Winston 2009	1.83	0.22	10	1.92	0.16	10	2.4%	-0.45 [-1.34, 0.44]
Total (95% CI)			**766**			**441**	**100.0%**	**-0.11 [-0.26, 0.03]**

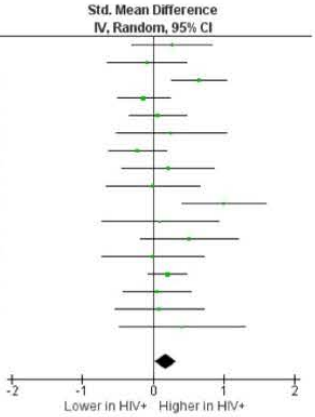
Heterogeneity: Tau² = 0.02; Chi² = 21.00, df = 16 (P = 0.18); I² = 24%
Test for overall effect: Z = 1.51 (P = 0.13)



Cho

Study or Subgroup	HIV+ Mean	HIV+ SD	HIV+ Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bairwa 2016	1.68	0.28	20	1.62	0.17	30	5.4%	0.27 [-0.30, 0.84]
Bladowska 2013	0.77	0.12	41	0.78	0.1	18	5.6%	-0.09 [-0.64, 0.47]
Chang 2004	0.81	0.13	100	0.73	0.1	37	9.0%	0.65 [0.26, 1.03]
Cysique-BL 2018	1.93	0.41	84	1.98	0.29	42	9.4%	-0.13 [-0.50, 0.24]
Cysique-FU 2018	1.91	0.42	73	1.88	0.52	35	8.5%	0.07 [-0.34, 0.47]
Ernst 2000	2.36	0.28	14	2.28	0.33	12	3.3%	0.25 [-0.52, 1.03]
Ernst 2010	1.6	0.37	45	1.68	0.34	46	8.3%	-0.22 [-0.64, 0.19]
Kallianpur 2013	0.27	0.05	35	0.26	0.03	12	4.3%	0.21 [-0.44, 0.87]
Koltowska 2010	0.77	0.11	25	0.77	0.12	14	4.3%	0.00 [-0.65, 0.65]
Lee 2003	0.87	0.17	38	0.72	0.08	18	5.0%	1.00 [0.41, 1.59]
Pulliam 2011	1.65	0.2	30	1.63	0.22	7	2.9%	0.10 [-0.73, 0.92]
Roc 2007	0.72	0.04	45	0.7	0.03	10	3.9%	0.51 [-0.18, 1.20]
Sailasuta 2012	0.23	0.02	26	0.23	0.01	10	3.6%	0.00 [-0.73, 0.73]
Taylor 2007	1.69	0.4	106	1.62	0.29	99	12.5%	0.20 [-0.08, 0.47]
Valcour 2015	2.2	0.38	42	2.18	0.26	27	6.8%	0.06 [-0.43, 0.54]
VonGiesen 2001	0.74	0.1	32	0.73	0.13	14	4.6%	0.09 [-0.54, 0.72]
Winston 2009	0.9	0.1	10	0.84	0.17	10	2.6%	0.41 [-0.48, 1.30]
Total (95% CI)			**766**			**441**	**100.0%**	**0.18 [0.02, 0.33]**

Heterogeneity: Tau² = 0.03; Chi² = 22.82, df = 16 (P = 0.12); I² = 30%
Test for overall effect: Z = 2.28 (P = 0.02)



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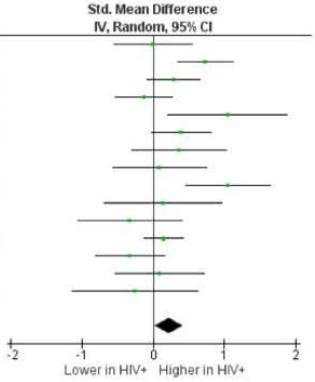
Study or Subgroup	HIV+ Mean	HIV+ SD	HIV+ Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bladowska 2013	0.54	0.1	41	0.54	0.12	18	6.6%	0.00 [-0.55, 0.55]
Chang 2004	0.57	0.13	100	0.48	0.1	37	9.0%	0.73 [0.34, 1.12]
Cysique-BL 2018	1.46	0.47	84	1.34	0.25	42	9.2%	0.29 [-0.08, 0.66]
Cysique-FU 2018	1.4	0.52	73	1.47	0.6	35	8.7%	-0.13 [-0.53, 0.28]
Ernst 2000	9.52	2.14	14	7.63	1.13	12	4.1%	1.05 [0.21, 1.88]
Ernst 2010	3.71	1.28	45	3.3	0.75	46	8.5%	0.39 [-0.03, 0.80]
Kallianpur 2013	0.55	0.61	35	0.35	0.23	12	5.5%	0.36 [-0.30, 1.02]
Koltowska 2010	0.53	0.1	25	0.52	0.11	14	5.5%	0.09 [-0.56, 0.75]
Lee 2003	0.59	0.14	38	0.46	0.07	18	6.2%	1.05 [0.45, 1.64]
Pulliam 2011	2.82	0.61	30	2.73	0.81	7	4.1%	0.14 [-0.69, 0.96]
Sailasuta 2012	0.56	0.09	26	0.59	0.09	10	4.8%	-0.33 [-1.06, 0.41]
Taylor 2007	4.77	1.47	106	4.57	1.17	99	10.7%	0.15 [-0.12, 0.42]
Valcour 2015	5.36	1.18	42	5.72	0.95	27	7.5%	-0.32 [-0.81, 0.16]
VonGiesen 2001	0.53	0.09	32	0.52	0.14	14	5.8%	0.09 [-0.54, 0.72]
Winston 2009	3.34	0.34	10	3.43	0.34	10	3.7%	-0.25 [-1.13, 0.63]
Total (95% CI)			**701**			**401**	**100.0%**	**0.22 [0.02, 0.42]**

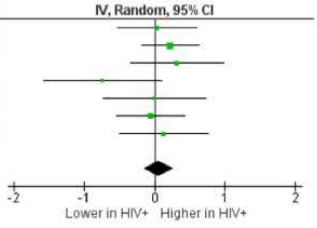
Heterogeneity: Tau² = 0.08; Chi² = 30.89, df = 14 (P = 0.006); I² = 55%
Test for overall effect: Z = 2.18 (P = 0.03)



Glx

Study or Subgroup	HIV+ Mean	HIV+ SD	HIV+ Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bairwa 2016	14.12	3.6	20	13.99	2.89	30	14.6%	0.04 [-0.53, 0.61]
Ernst 2010	4.1	1.37	45	3.83	0.95	46	27.5%	0.23 [-0.18, 0.64]
Kallianpur 2013	0.93	0.36	35	0.82	0.27	12	10.8%	0.32 [-0.34, 0.98]
Pulliam 2011	4.86	0.68	30	5.37	0.67	7	6.6%	-0.74 [-1.58, 0.11]
Sailasuta 2012	1.81	0.23	26	1.81	0.22	10	8.8%	0.00 [-0.73, 0.73]
Valcour 2015	18.49	2.97	42	18.64	2.45	27	20.0%	-0.05 [-0.54, 0.43]
VonGiesen 2001	0.84	0.32	32	0.8	0.19	14	11.8%	0.14 [-0.49, 0.77]
Total (95% CI)			**230**			**146**	**100.0%**	**0.06 [-0.16, 0.28]**

Heterogeneity: Tau² = 0.00; Chi² = 4.96, df = 6 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.54 (P = 0.59)



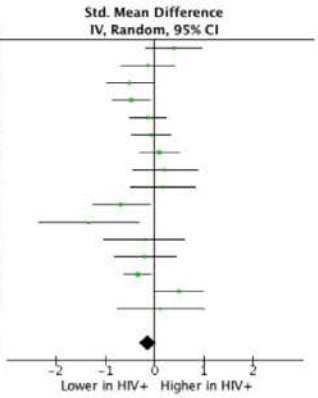
B

Frontal White Matter

NAA

Study or Subgroup	HIV+ Mean	HIV+ SD	HIV+ Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bairwa 2016	10.67	3.8	20	9.29	3.11	30	5.8%	0.40 [-0.17, 0.97]
Bladowska 2013	1.87	0.16	41	1.9	0.33	18	6.0%	-0.13 [-0.69, 0.42]
Boban 2017	1.76	0.52	31	2.02	0.51	41	7.1%	-0.50 [-0.97, -0.03]
Chang 2004	1.73	0.2	100	1.82	0.17	37	8.6%	-0.47 [-0.85, -0.08]
Cysique-BL 2018	4.45	0.39	84	4.5	0.35	42	8.8%	-0.13 [-0.50, 0.24]
Cysique-FU 2018	4.35	0.56	73	4.39	0.74	35	8.2%	-0.06 [-0.47, 0.34]
Ernst 2010	7.85	0.88	45	7.75	1.02	46	8.1%	0.10 [-0.31, 0.52]
Kallianpur 2013	1.38	0.09	35	1.36	0.1	12	4.9%	0.21 [-0.44, 0.87]
Koltowska 2010	1.74	0.31	25	1.69	0.18	14	4.9%	0.18 [-0.48, 0.84]
Lee 2003	1.69	0.18	38	1.81	0.17	18	5.8%	-0.67 [-1.24, -0.09]
Lentz 2009	9.58	0.82	10	10.52	0.45	9	2.5%	-1.34 [-2.36, -0.32]
Pulliam 2011	5.55	0.69	30	5.68	0.3	7	3.5%	-0.20 [-1.02, 0.63]
Tarasow 2004	1.8	0.35	14	1.86	0.3	32	5.2%	-0.19 [-0.82, 0.44]
Taylor 2007	7.63	1.08	106	7.95	0.82	99	10.6%	-0.33 [-0.61, -0.06]
Valcour 2015	12.17	1.17	40	11.61	1.01	28	6.9%	0.50 [0.01, 0.99]
Winston 2009	1.65	0.25	10	1.61	0.35	10	3.2%	0.13 [-0.75, 1.00]
Total (95% CI)			**702**			**478**	**100.0%**	**-0.14 [-0.31, 0.04]**

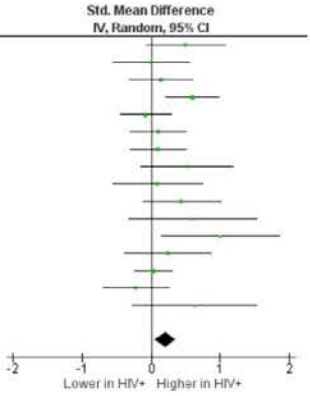
Heterogeneity: Tau² = 0.06; Chi² = 29.19, df = 15 (P = 0.02); I² = 49%
Test for overall effect: Z = 1.48 (P = 0.14)



Cho

Study or Subgroup	HIV+ Mean	HIV+ SD	HIV+ Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bairwa 2016	2.5	0.99	20	2.08	0.7	30	5.1%	0.50 [-0.08, 1.07]
Bladowska 2013	1.14	0.25	41	1.14	0.28	18	5.4%	0.00 [-0.55, 0.55]
Boban 2017	1.03	0.21	31	1	0.2	41	7.1%	0.15 [-0.32, 0.61]
Chang 2004	1.12	0.17	100	1.02	0.15	37	9.4%	0.60 [0.22, 0.99]
Cysique-BL 2018	2.37	0.34	84	2.4	0.42	42	9.9%	-0.08 [-0.45, 0.29]
Cysique-FU 2018	2.44	0.4	73	2.4	0.34	35	8.8%	0.10 [-0.30, 0.51]
Ernst 2010	2.35	0.46	45	2.31	0.34	46	8.6%	0.10 [-0.31, 0.51]
Kallianpur 2013	0.27	0.04	35	0.25	0.03	12	4.0%	0.52 [-0.14, 1.19]
Koltowska 2010	1.04	0.21	25	1.02	0.21	14	4.1%	0.09 [-0.56, 0.75]
Lee 2003	1.11	0.19	38	1.03	0.15	18	5.2%	0.44 [-0.12, 1.01]
Lentz 2009	1.75	0.19	10	1.64	0.15	9	2.2%	0.61 [-0.32, 1.54]
Pulliam 2011	1.33	0.19	30	1.13	0.22	7	2.5%	1.00 [0.14, 1.86]
Tarasow 2004	0.84	0.31	14	0.79	0.13	32	4.4%	0.24 [-0.39, 0.88]
Taylor 2007	1.6	0.28	106	1.59	0.27	99	14.1%	0.04 [-0.24, 0.31]
Valcour 2015	2.86	0.32	40	2.93	0.31	28	6.7%	-0.22 [-0.70, 0.27]
Winston 2009	1.07	0.1	10	0.99	0.14	10	2.3%	0.63 [-0.27, 1.53]
Total (95% CI)			**702**			**478**	**100.0%**	**0.20 [0.06, 0.35]**

Heterogeneity: Tau² = 0.02; Chi² = 19.37, df = 15 (P = 0.20); I² = 23%
Test for overall effect: Z = 2.80 (P = 0.005)



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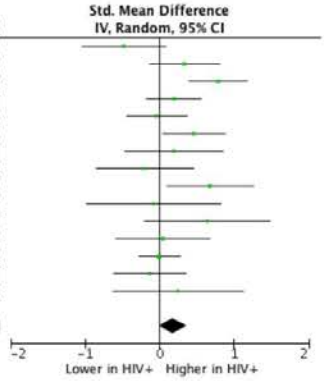
Study or Subgroup	HIV+ Mean	HIV+ SD	HIV+ Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bladowska 2013	0.69	0.13	41	0.77	0.23	18	6.2%	-0.47 [-1.04, 0.09]
Boban 2017	0.54	0.2	31	0.48	0.16	41	7.6%	0.33 [-0.14, 0.80]
Chang 2004	0.69	0.11	100	0.61	0.07	37	9.0%	0.79 [0.40, 1.18]
Cysique-BL 2018	1.14	0.25	84	1.09	0.28	42	9.3%	0.19 [-0.18, 0.56]
Cysique-FU 2018	1.13	0.25	73	1.14	0.2	35	8.7%	-0.04 [-0.45, 0.36]
Ernst 2010	4.26	0.96	45	3.85	0.81	46	8.5%	0.46 [0.04, 0.87]
Kallianpur 2013	0.66	0.16	35	0.63	0.13	12	5.1%	0.19 [-0.46, 0.85]
Koltowska 2010	0.64	0.11	25	0.66	0.07	14	5.1%	-0.20 [-0.86, 0.46]
Lee 2003	0.69	0.15	38	0.6	0.07	18	6.1%	0.68 [0.11, 1.26]
Lentz 2009	4.84	1.2	10	4.94	1.29	9	3.2%	-0.08 [-0.98, 0.82]
Pulliam 2011	5.24	0.5	30	4.9	0.61	7	3.6%	0.64 [-0.20, 1.48]
Tarasow 2004	0.63	0.26	14	0.62	0.18	32	5.4%	0.05 [-0.58, 0.68]
Taylor 2007	4.4	1.21	106	4.4	1.73	99	11.3%	0.00 [-0.27, 0.27]
Valcour 2015	7.99	1.63	40	8.19	1.29	28	7.4%	-0.13 [-0.62, 0.35]
Winston 2009	4.1	0.89	10	3.9	0.66	10	3.4%	0.24 [-0.64, 1.13]
Total (95% CI)			**682**			**448**	**100.0%**	**0.18 [-0.00, 0.37]**

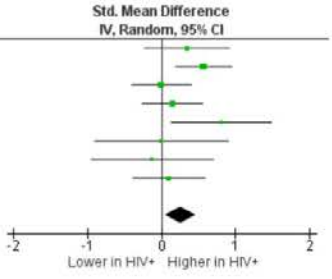
Heterogeneity: Tau² = 0.06; Chi² = 27.05, df = 14 (P = 0.02); I² = 48%
Test for overall effect: Z = 1.95 (P = 0.05)



Glx

Study or Subgroup	HIV+ Mean	HIV+ SD	HIV+ Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bairwa 2016	17.08	5.6	20	15	6.06	30	10.8%	0.35 [-0.22, 0.92]
Cysique-BL 2018	1.71	0.39	84	1.5	0.31	42	20.3%	0.57 [0.19, 0.95]
Cysique-FU 2018	1.57	0.42	73	1.57	0.43	35	18.5%	0.00 [-0.40, 0.40]
Ernst 2010	5.36	1	45	5.21	0.95	46	17.9%	0.15 [-0.26, 0.56]
Kallianpur 2013	1.01	0.13	35	0.88	0.22	12	8.0%	0.81 [0.14, 1.49]
Lentz 2009	9.04	1.17	10	9.04	1.32	9	4.8%	0.00 [-0.90, 0.90]
Pulliam 2011	4.91	0.76	30	5	0.21	7	5.7%	-0.13 [-0.95, 0.70]
Valcour 2015	14.15	2.26	40	13.93	1.9	28	14.1%	0.10 [-0.38, 0.59]
Total (95% CI)			**337**			**209**	**100.0%**	**0.25 [0.05, 0.46]**

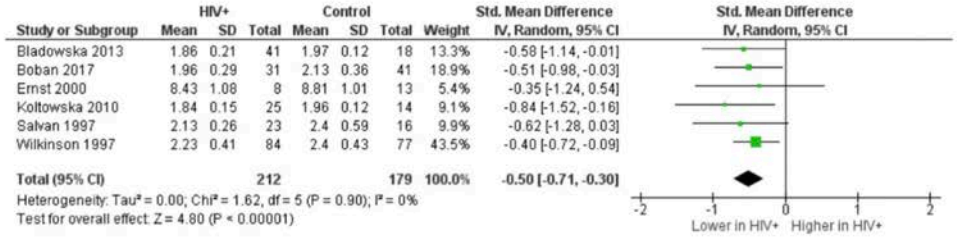
Heterogeneity: Tau² = 0.02; Chi² = 8.71, df = 7 (P = 0.27); I² = 20%
Test for overall effect: Z = 2.42 (P = 0.02)



C

Parietal White Matter

NAA



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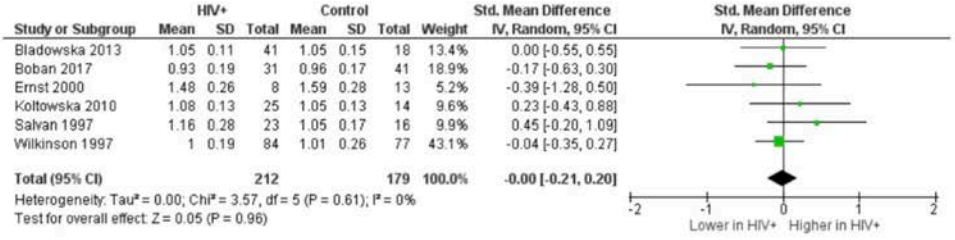

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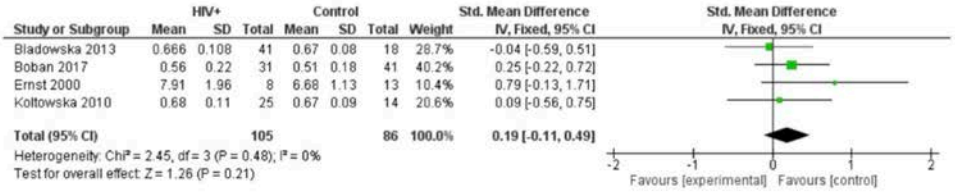


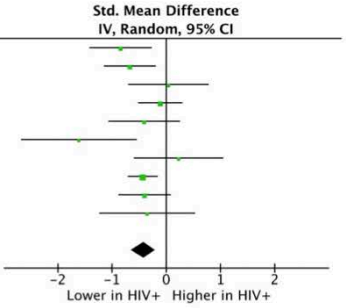
D

Frontal Gray Matter

NAA

Study or Subgroup	PLWH Mean	SD	Total	Controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bladowska 2013	1.54	0.24	41	1.74	0.22	18	9.9%	−0.84 [−1.42, −0.27]
Boban 2017	1.75	0.43	31	2.03	0.4	41	12.5%	−0.67 [−1.15, −0.19]
Ernst 2000	8.56	0.56	15	8.54	0.38	13	6.8%	0.04 [−0.70, 0.78]
Ernst 2010	7.7	0.91	45	7.8	0.88	46	14.8%	−0.11 [−0.52, 0.30]
Koltowska 2010	1.54	0.2	25	1.62	0.18	14	8.2%	−0.41 [−1.07, 0.26]
Lentz 2009	8.62	1.14	10	10.14	0.51	9	3.7%	−1.61 [−2.68, −0.54]
Pulliam 2011	7.53	0.93	30	7.3	1.24	7	5.8%	0.23 [−0.60, 1.05]
Taylor 2007	7.31	0.74	106	7.66	0.87	99	20.7%	−0.43 [−0.71, −0.16]
Valcour 2015	9	1.35	42	9.51	1.12	28	12.4%	−0.40 [−0.88, 0.08]
Winston 2009	1.48	0.17	10	1.63	0.55	10	5.2%	−0.35 [−1.24, 0.53]
Total (95% CI)			**355**			**285**	**100.0%**	**−0.42 [−0.64, −0.20]**

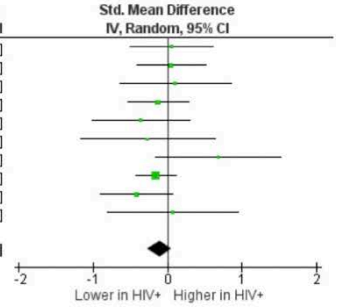
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 13.94$, df = 9 (P = 0.12); $I^2 = 35\%$
Test for overall effect: Z = 3.72 (P = 0.0002)



Cho

Study or Subgroup	HIV+ Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bladowska 2013	0.83	0.18	41	0.82	0.2	18	8.3%	0.05 [-0.50, 0.61]
Boban 2017	0.99	0.19	31	0.98	0.19	41	11.7%	0.05 [-0.41, 0.52]
Ernst 2000	2.16	0.27	15	2.13	0.28	13	4.6%	0.11 [-0.64, 0.85]
Ernst 2010	2.16	0.35	45	2.2	0.27	46	15.0%	-0.13 [-0.54, 0.28]
Koltowska 2010	0.8	0.15	25	0.86	0.19	14	5.8%	-0.36 [-1.02, 0.30]
Lentz 2009	1.66	0.51	10	1.77	0.21	9	3.1%	-0.26 [-1.17, 0.64]
Pulliam 2011	1.69	0.25	30	1.51	0.3	7	3.6%	0.68 [-0.16, 1.52]
Taylor 2007	1.3	0.25	106	1.34	0.26	99	33.7%	-0.16 [-0.43, 0.12]
Valcour 2015	2	0.27	42	2.12	0.31	28	10.9%	-0.41 [-0.90, 0.07]
Winston 2009	0.71	0.13	10	0.7	0.14	10	3.3%	0.07 [-0.81, 0.95]
Total (95% CI)			**355**			**285**	**100.0%**	**-0.10 [-0.26, 0.06]**

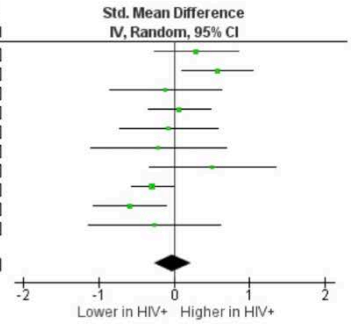
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.96$, df = 9 (P = 0.64); $I^2 = 0\%$
Test for overall effect: Z = 1.27 (P = 0.20)



ml

Study or Subgroup	HIV+ Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bladowska 2013	0.71	0.19	41	0.66	0.11	18	10.5%	0.29 [-0.27, 0.85]
Boban 2017	0.58	0.24	31	0.47	0.14	41	12.2%	0.57 [0.10, 1.05]
Ernst 2000	0.83	0.08	15	0.84	0.09	13	7.5%	-0.11 [-0.86, 0.63]
Ernst 2010	5.07	1.01	45	5	1.02	46	13.8%	0.07 [-0.34, 0.48]
Koltowska 2010	0.7	0.14	25	0.71	0.12	14	8.8%	-0.07 [-0.73, 0.58]
Lentz 2009	5.61	1.52	10	5.88	0.84	9	5.7%	-0.21 [-1.11, 0.70]
Pulliam 2011	5.38	0.72	30	5.03	0.33	7	6.4%	0.51 [-0.32, 1.34]
Taylor 2007	3.93	0.8	106	4.16	0.78	99	17.3%	-0.29 [-0.57, -0.01]
Valcour 2015	6.38	0.97	44	6.93	0.83	28	12.0%	-0.59 [-1.08, -0.11]
Winston 2009	3.7	0.98	10	4	1.2	10	5.9%	-0.26 [-1.14, 0.62]
Total (95% CI)			**357**			**285**	**100.0%**	**-0.02 [-0.27, 0.23]**

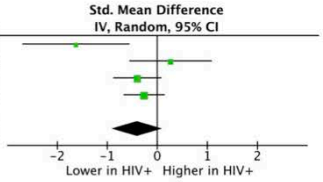
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 18.15$, df = 9 (P = 0.03); $I^2 = 50\%$
Test for overall effect: Z = 0.16 (P = 0.87)



Glx

Study or Subgroup	HIV+ Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Lentz 2009	13.71	2.15	10	16.59	0.93	9	14.8%	−1.63 [−2.70, −0.56]
Pulliam 2011	4.9	0.8	30	4.68	0.86	7	20.3%	0.27 [−0.56, 1.09]
Valcour 2015	16	2.33	42	16.89	2.02	28	31.2%	−0.40 [−0.88, 0.09]
Ernst 2010	7.09	1.02	45	7.37	1.09	46	33.7%	−0.26 [−0.68, 0.15]
Total (95% CI)			**127**			**90**	**100.0%**	**−0.40 [−0.91, 0.11]**

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 7.81$, df = 3 (P = 0.05); $I^2 = 62\%$
Test for overall effect: Z = 1.54 (P = 0.12)



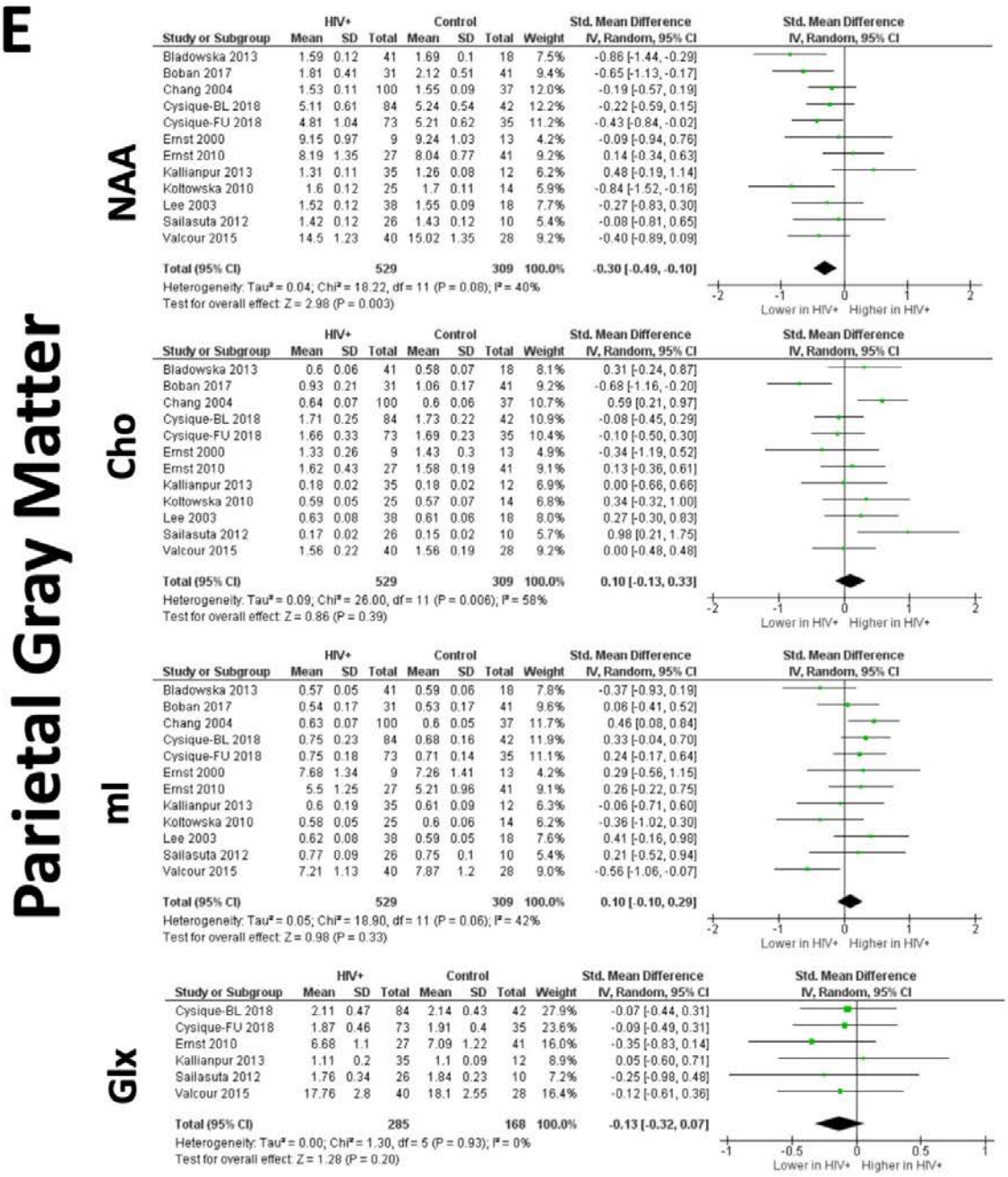


Figure e-1. Study effect sizes of brain metabolites between chronic PWH and controls in the primary meta-analysis

(**A**) Basal Ganglia; (**B**) Frontal White Matter; (**C**) Parietal White Matter; (**D**) Frontal Gray Matter; (**E**) Parietal Gray Matter. Metabolites: NAA, N-acetyl aspartate; Cho, choline; mI, myo-Inositol; Glx, glutamate (Glu), or a combination of Glu and glutamine (Gln).

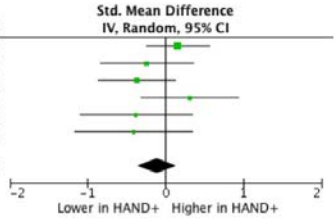
A

Basal Ganglia

NAA

Study or Subgroup	HAND+ Mean	HAND+ SD	HAND+ Total	HAND− Mean	HAND− SD	HAND− Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2004	1.42	0.21	61	1.39	0.16	39	29.1%	0.15 [−0.25, 0.56]
Ernst 2010	7.34	0.85	18	7.55	0.83	27	15.1%	−0.25 [−0.84, 0.35]
Mohamed 2010	7.13	1.35	65	7.6	1	21	20.9%	−0.37 [−0.86, 0.13]
Roc 2007	1.22	0.1	30	1.19	0.08	15	14.1%	0.31 [−0.31, 0.94]
Sailasuta 2016	9.04	1.48	9	9.63	1.54	41	10.7%	−0.38 [−1.11, 0.35]
VonGiesen 2001	1.49	0.16	22	1.55	0.09	10	10.0%	−0.41 [−1.17, 0.35]
Total (95% CI)			**205**			**153**	**100.0%**	**−0.11 [−0.35, 0.14]**

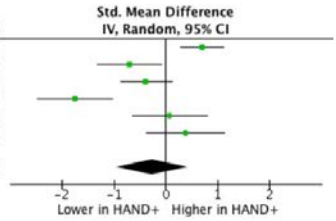
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.78$, df = 5 (P = 0.33); $I^2 = 13\%$
Test for overall effect: Z = 0.83 (P = 0.40)



Cho

Study or Subgroup	HAND+ Mean	HAND+ SD	HAND+ Total	HAND− Mean	HAND− SD	HAND− Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2004	0.85	0.15	61	0.76	0.08	39	18.1%	0.70 [0.29, 1.11]
Ernst 2010	1.45	0.34	18	1.7	0.36	27	16.8%	−0.70 [−1.31, −0.08]
Mohamed 2010	1.98	0.35	65	2.11	0.3	21	17.6%	−0.38 [−0.88, 0.12]
Roc 2007	0.71	0.02	30	0.76	0.04	15	15.9%	−1.75 [−2.47, −1.02]
Sailasuta 2016	2.3	0.46	9	2.27	0.34	41	16.0%	0.08 [−0.64, 0.80]
VonGiesen 2001	0.76	0.11	22	0.72	0.08	10	15.7%	0.38 [−0.37, 1.14]
Total (95% CI)			**205**			**153**	**100.0%**	**−0.26 [−0.96, 0.43]**

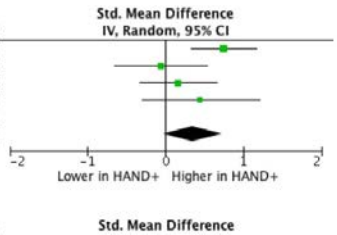
Heterogeneity: $Tau^2 = 0.65$; $Chi^2 = 40.81$, df = 5 (P < 0.00001); $I^2 = 88\%$
Test for overall effect: Z = 0.74 (P = 0.46)



mI

Study or Subgroup	HAND+ Mean	HAND+ SD	HAND+ Total	HAND− Mean	HAND− SD	HAND− Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2004	0.61	0.13	61	0.52	0.1	39	32.1%	0.75 [0.33, 1.16]
Ernst 2010	3.66	1.1	18	3.74	1.4	27	22.9%	−0.06 [−0.66, 0.54]
Mohamed 2010	3.21	0.75	65	3.08	0.87	21	27.9%	0.17 [−0.33, 0.66]
VonGiesen 2001	0.54	0.09	22	0.5	0.08	10	17.1%	0.45 [−0.31, 1.20]
Total (95% CI)			**166**			**97**	**100.0%**	**0.35 [−0.03, 0.73]**

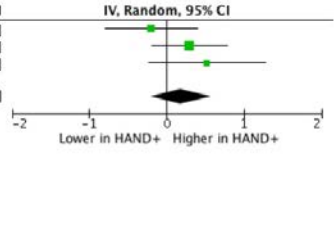
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 5.88$, df = 3 (P = 0.12); $I^2 = 49\%$
Test for overall effect: Z = 1.79 (P = 0.07)



Glx

Study or Subgroup	HAND+ Mean	HAND+ SD	HAND+ Total	HAND− Mean	HAND− SD	HAND− Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ernst 2010	3.93	1.48	18	4.21	1.3	27	33.3%	−0.20 [−0.80, 0.40]
Mohamed 2010	12.38	2.27	65	11.68	2.57	21	44.3%	0.30 [−0.20, 0.79]
VonGiesen 2001	0.89	0.35	22	0.72	0.23	10	22.4%	0.52 [−0.24, 1.28]
Total (95% CI)			**105**			**58**	**100.0%**	**0.18 [−0.21, 0.57]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.53$, df = 2 (P = 0.28); $I^2 = 21\%$
Test for overall effect: Z = 0.91 (P = 0.36)



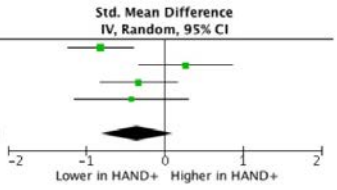
B

Frontal White Matter

NAA

Study or Subgroup	HAND+ Mean	SD	Total	HAND− Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2004	1.67	0.2	61	1.82	0.15	39	29.6%	-0.82 [-1.23, -0.40]
Ernst 2010	7.99	0.68	18	7.75	0.99	27	23.6%	0.27 [-0.33, 0.87]
Mohamed 2010	7.34	1.01	65	7.67	0.93	21	27.0%	-0.33 [-0.82, 0.16]
Sailasuta 2016	11.27	1.15	9	11.82	1.31	41	19.9%	-0.42 [-1.15, 0.31]
Total (95% CI)			**153**			**128**	**100.0%**	**-0.35 [-0.81, 0.11]**

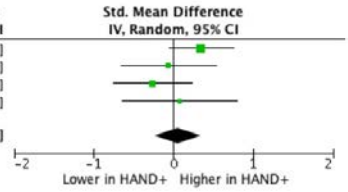
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 8.65$, df = 3 (P = 0.03); $I^2 = 65\%$
Test for overall effect: Z = 1.49 (P = 0.14)



Cho

Study or Subgroup	HAND+ Mean	SD	Total	HAND− Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2004	1.14	0.19	61	1.08	0.14	39	37.2%	0.35 [-0.06, 0.75]
Ernst 2010	2.33	0.59	18	2.36	0.36	27	20.4%	-0.06 [-0.66, 0.53]
Mohamed 2010	1.81	0.32	65	1.9	0.39	21	27.7%	-0.26 [-0.76, 0.23]
Sailasuta 2016	2.92	0.31	9	2.89	0.38	41	14.7%	0.08 [-0.64, 0.80]
Total (95% CI)			**153**			**128**	**100.0%**	**0.05 [-0.24, 0.35]**

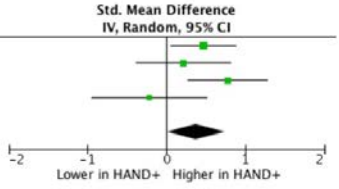
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.73$, df = 3 (P = 0.29); $I^2 = 20\%$
Test for overall effect: Z = 0.36 (P = 0.72)



mI

Study or Subgroup	HAND+ Mean	SD	Total	HAND− Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2004	0.71	0.13	61	0.66	0.05	39	33.1%	0.47 [0.06, 0.87]
Ernst 2010	4.39	1.15	18	4.18	0.83	27	22.4%	0.21 [-0.39, 0.81]
Mohamed 2010	4.01	0.81	65	3.4	0.67	21	27.0%	0.78 [0.27, 1.28]
Sailasuta 2016	7.98	0.89	9	8.24	1.21	41	17.5%	-0.22 [-0.94, 0.50]
Total (95% CI)			**153**			**128**	**100.0%**	**0.37 [0.01, 0.74]**

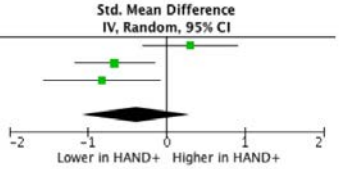
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 5.42$, df = 3 (P = 0.14); $I^2 = 45\%$
Test for overall effect: Z = 2.01 (P = 0.04)



Glx

Study or Subgroup	HAND+ Mean	SD	Total	HAND− Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Ernst 2010	5.55	1.02	18	5.24	0.99	27	33.7%	0.30 [-0.30, 0.90]
Mohamed 2010	8.65	2.14	65	10	1.62	21	36.6%	-0.66 [-1.16, -0.16]
Sailasuta 2016	8.96	1.8	9	10.55	1.92	41	29.7%	-0.82 [-1.56, -0.08]
Total (95% CI)			**92**			**89**	**100.0%**	**-0.38 [-1.07, 0.30]**

Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 7.56$, df = 2 (P = 0.02); $I^2 = 74\%$
Test for overall effect: Z = 1.10 (P = 0.27)



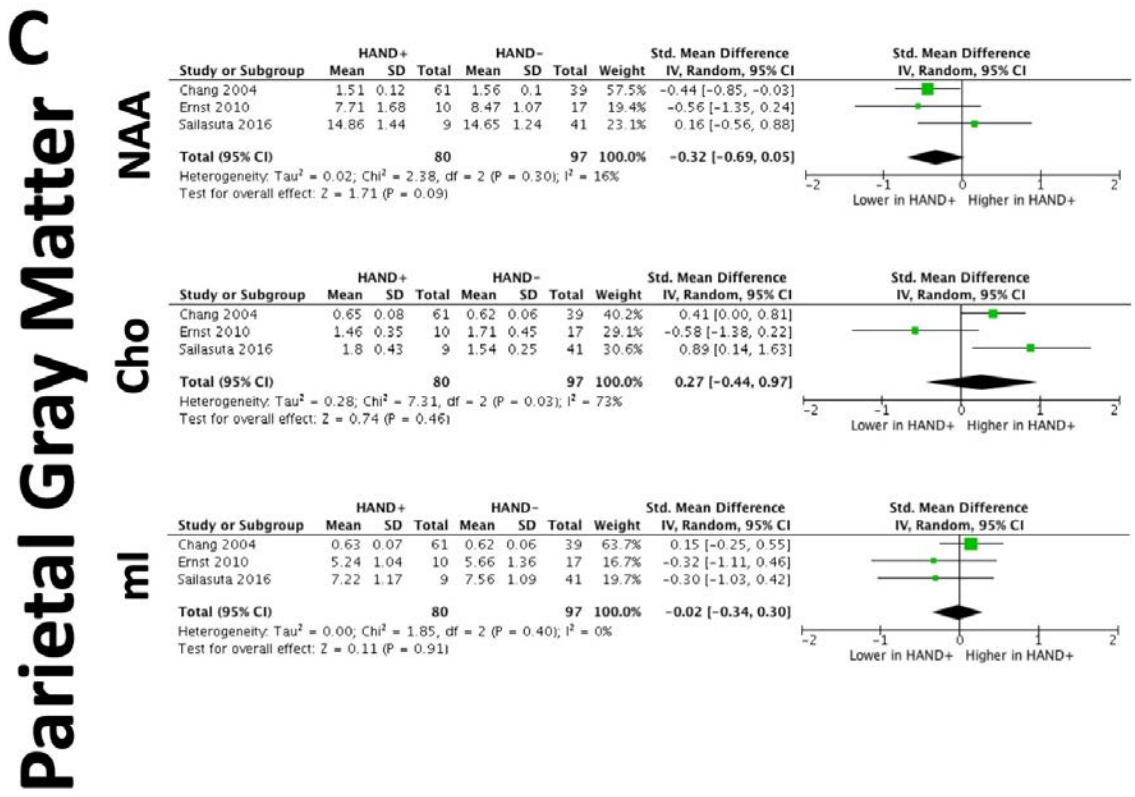


Figure e-2. Study effect sizes of brain metabolites between cognitively impaired PWH and cognitively normal PWH in the primary meta-analysis

(**A**) Basal Ganglia; (**B**) Frontal White Matter; (**C**) Parietal Gray Matter. Metabolites: NAA, N-acetyl aspartate; Cho, choline; mI, myo-Inositol; Glx, glutamate (Glu), or a combination of Glu and glutamine (Gln).

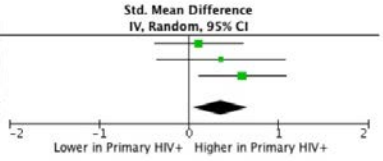
A

Basal Ganglia

NAA

Study or Subgroup	Primary HIV+ Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2002	8.5	0.94	45	8.4	0.8	25	40.6%	0.11 [-0.38, 0.60]
Sailasuta 2012	1.13	0.14	31	1.08	0.13	10	18.9%	0.36 [-0.36, 1.07]
Valcour 2015	10.41	1.47	44	9.55	1.34	27	40.5%	0.60 [0.11, 1.09]
Total (95% CI)			**120**			**62**	**100.0%**	**0.35 [0.04, 0.67]**

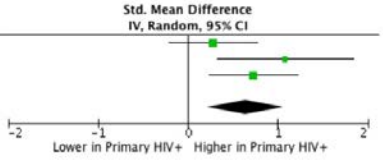
Heterogeneity: Tau² = 0.00; Chi² = 1.90, df = 2 (P = 0.39); I² = 0%
Test for overall effect: Z = 2.23 (P = 0.03)



Cho

Study or Subgroup	Primary HIV+ Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2002	2.2	0.4	45	2.1	0.25	25	38.7%	0.28 [-0.21, 0.77]
Sailasuta 2012	0.25	0.02	31	0.23	0.01	10	22.8%	1.08 [0.32, 1.83]
Valcour 2015	2.4	0.32	44	2.18	0.26	27	38.4%	0.73 [0.23, 1.22]
Total (95% CI)			**120**			**62**	**100.0%**	**0.63 [0.21, 1.06]**

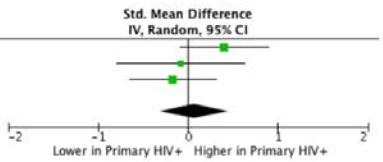
Heterogeneity: Tau² = 0.06; Chi² = 3.44, df = 2 (P = 0.18); I² = 42%
Test for overall effect: Z = 2.91 (P = 0.004)



mI

Study or Subgroup	Primary HIV+ Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2002	7	1.68	45	6.4	1.05	25	38.2%	0.40 [-0.09, 0.89]
Sailasuta 2012	0.58	0.13	31	0.59	0.09	10	22.3%	-0.08 [-0.79, 0.63]
Valcour 2015	5.51	1.35	44	5.72	0.95	27	39.6%	-0.17 [-0.65, 0.31]
Total (95% CI)			**120**			**62**	**100.0%**	**0.07 [-0.31, 0.44]**

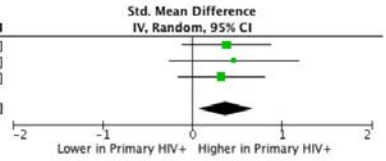
Heterogeneity: Tau² = 0.03; Chi² = 2.84, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 0.35 (P = 0.73)



Glx

Study or Subgroup	Primary HIV+ Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2002	18.8	3.15	45	17.6	2.95	25	39.8%	0.39 [-0.11, 0.88]
Sailasuta 2012	1.96	0.34	31	1.81	0.22	10	18.6%	0.46 [-0.26, 1.19]
Valcour 2015	19.53	2.87	44	18.64	2.45	27	41.6%	0.32 [-0.16, 0.81]
Total (95% CI)			**120**			**62**	**100.0%**	**0.37 [0.06, 0.69]**

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)



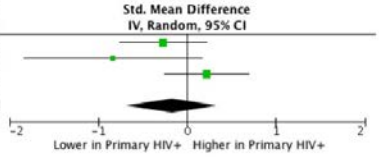
B

Frontal White Matter

NAA

Study or Subgroup	Primary HIV+ Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2002	7.2	0.74	45	7.4	0.7	25	40.3%	-0.27 [-0.76, 0.22]
Lentz 2009	10.02	0.68	8	10.52	0.45	9	18.4%	-0.83 [-1.84, 0.17]
Valcour 2015	11.88	1.33	44	11.61	1.01	28	41.3%	0.22 [-0.26, 0.69]
Total (95% CI)			**97**			**62**	**100.0%**	**-0.17 [-0.68, 0.34]**

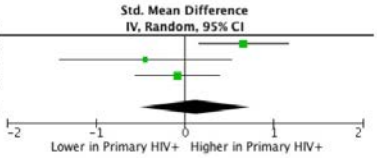
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 4.26$, df = 2 (P = 0.12); $I^2 = 53\%$
Test for overall effect: Z = 0.66 (P = 0.51)



Cho

Study or Subgroup	Primary HIV+ Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2002	1.8	0.34	45	1.6	0.2	25	38.1%	0.66 [0.16, 1.17]
Lentz 2009	1.52	0.34	8	1.64	0.15	9	22.8%	-0.44 [-1.41, 0.52]
Valcour 2015	2.9	0.39	44	2.93	0.31	28	39.1%	-0.08 [-0.56, 0.39]
Total (95% CI)			**97**			**62**	**100.0%**	**0.12 [-0.50, 0.74]**

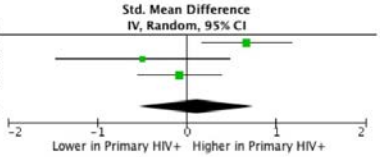
Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 6.33$, df = 2 (P = 0.04); $I^2 = 68\%$
Test for overall effect: Z = 0.37 (P = 0.71)



mI

Study or Subgroup	Primary HIV+ Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2002	7.8	1.74	45	6.7	1.35	25	37.9%	0.67 [0.17, 1.18]
Lentz 2009	4.28	1.24	8	4.94	1.29	9	23.2%	-0.49 [-1.47, 0.48]
Valcour 2015	8.07	1.59	44	8.19	1.29	28	38.9%	-0.08 [-0.55, 0.39]
Total (95% CI)			**97**			**62**	**100.0%**	**0.11 [-0.53, 0.75]**

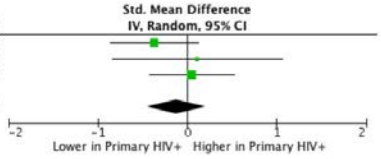
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 6.73$, df = 2 (P = 0.03); $I^2 = 70\%$
Test for overall effect: Z = 0.33 (P = 0.74)



Glx

Study or Subgroup	Primary HIV+ Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2002	11.1	1.68	45	11.8	2.15	25	42.6%	-0.37 [-0.87, 0.12]
Lentz 2009	9.19	1.3	8	9.04	1.32	9	11.4%	0.11 [-0.84, 1.06]
Valcour 2015	14.04	2.45	44	13.93	1.9	28	46.1%	0.05 [-0.43, 0.52]
Total (95% CI)			**97**			**62**	**100.0%**	**-0.12 [-0.45, 0.20]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.71$, df = 2 (P = 0.43); $I^2 = 0\%$
Test for overall effect: Z = 0.75 (P = 0.45)



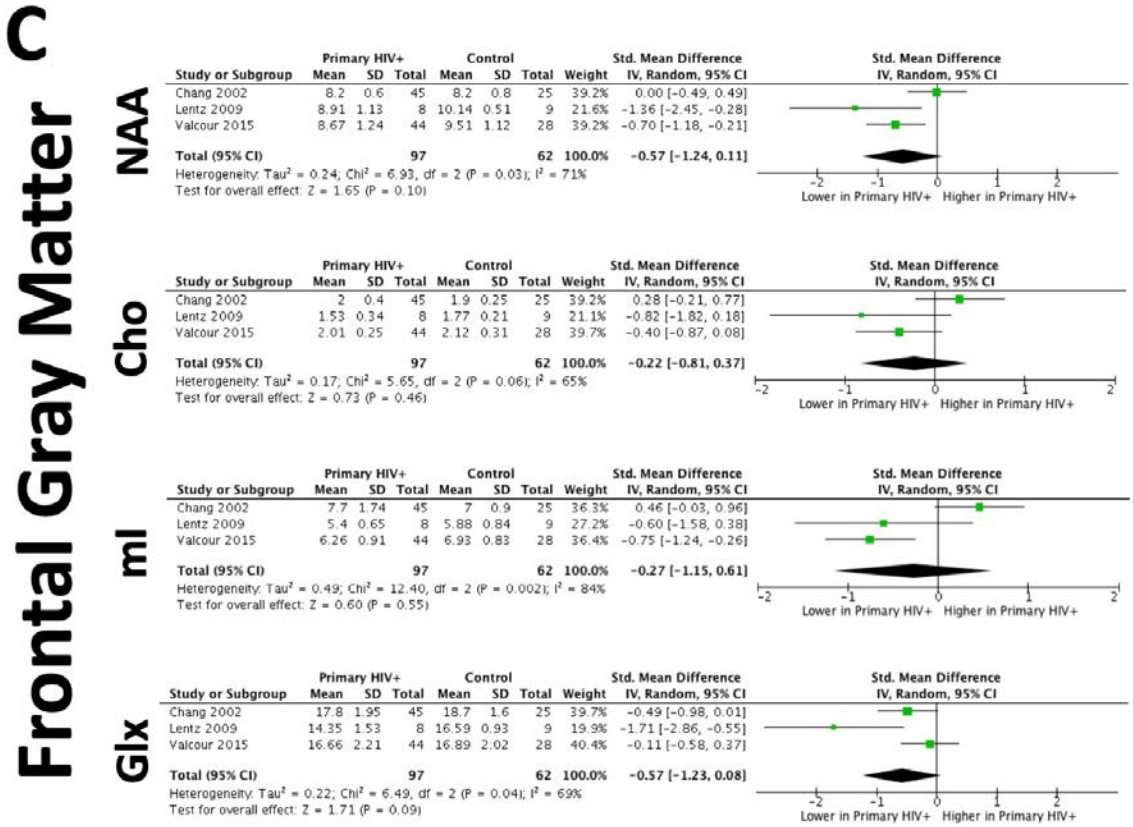


Figure e-3. Study effect sizes of brain metabolites between acute/early infection PWH and controls in the primary meta-analysis

(**A**) Basal Ganglia; (**B**) Frontal White Matter; (**C**) Frontal Gray Matter. Metabolites: NAA, N-acetyl aspartate; Cho, choline; mI, myo-Inositol; Glx, glutamate (Glu), or a combination of Glu and glutamine (Gln).

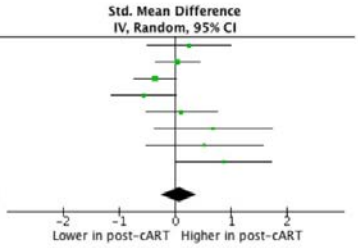
A

Basal Ganglia

NAA

Study or Subgroup	Post-cART Mean	SD	Total	Pre-cART Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 1999	8.8	0.75	14	8.57	0.99	14	10.9%	0.25 [-0.49, 1.00]
Mora-Peris: 2018	1.29	0.21	50	1.28	0.19	50	19.2%	0.05 [-0.34, 0.44]
Sailasuta 2016	9.52	1.53	50	10.02	1.28	59	19.5%	-0.35 [-0.73, 0.03]
Valcour cART 2015	9.51	1.54	24	10.38	1.49	24	14.3%	-0.56 [-1.14, 0.01]
Valcour cART+ 2015	10.63	1.86	18	10.44	1.48	20	13.0%	0.11 [-0.53, 0.75]
Winston Arm 1 2010	2.72	1.48	8	1.91	0.43	7	6.8%	0.68 [-0.38, 1.73]
Winston Arm 2 2010	2.78	0.82	7	2.27	0.98	8	7.0%	0.53 [-0.51, 1.57]
Winston Arm 3 2010	2.61	1.03	12	1.92	0.34	12	9.3%	0.87 [0.02, 1.71]
Total (95% CI)			**183**			**194**	**100.0%**	**0.07 [-0.25, 0.38]**

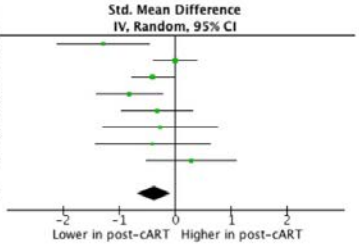
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 14.20$, df = 7 (P = 0.05); $I^2 = 51\%$
Test for overall effect: Z = 0.40 (P = 0.69)



Cho

Study or Subgroup	Post-cART Mean	SD	Total	Pre-cART Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 1999	0.81	0.12	14	0.95	0.09	14	9.4%	-1.28 [-2.11, -0.46]
Mora-Peris: 2018	0.26	0.05	50	0.26	0.05	50	20.0%	0.00 [-0.39, 0.39]
Sailasuta 2016	2.28	0.36	50	2.42	0.34	59	20.4%	-0.40 [-0.78, -0.02]
Valcour cART 2015	2.13	0.32	24	2.39	0.31	24	14.1%	-0.81 [-1.40, -0.22]
Valcour cART+ 2015	2.29	0.44	18	2.42	0.34	20	12.8%	-0.33 [-0.97, 0.32]
Winston Arm 1 2010	0.91	0.24	8	0.97	0.18	7	6.8%	-0.26 [-1.28, 0.76]
Winston Arm 2 2010	0.88	0.19	7	1.23	1.12	8	6.8%	-0.40 [-1.42, 0.63]
Winston Arm 3 2010	0.98	0.38	12	0.89	0.19	12	9.7%	0.29 [-0.52, 1.09]
Total (95% CI)			**183**			**194**	**100.0%**	**-0.37 [-0.68, -0.07]**

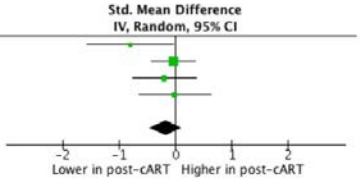
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 12.82$, df = 7 (P = 0.08); $I^2 = 45\%$
Test for overall effect: Z = 2.41 (P = 0.02)



mI

Study or Subgroup	Post-cART Mean	SD	Total	Pre-cART Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 1999	8	1.02	14	9.07	1.52	14	12.9%	-0.80 [-1.58, -0.03]
Mora-Peris: 2018	0.59	0.21	50	0.6	0.29	50	45.2%	-0.04 [-0.43, 0.35]
Valcour cART 2015	5.3	1.17	24	5.55	1.31	24	23.2%	-0.20 [-0.77, 0.37]
Valcour cART+ 2015	5.45	1.22	18	5.47	1.42	20	18.7%	-0.01 [-0.65, 0.62]
Total (95% CI)			**106**			**108**	**100.0%**	**-0.17 [-0.45, 0.11]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.22$, df = 3 (P = 0.36); $I^2 = 7\%$
Test for overall effect: Z = 1.17 (P = 0.24)



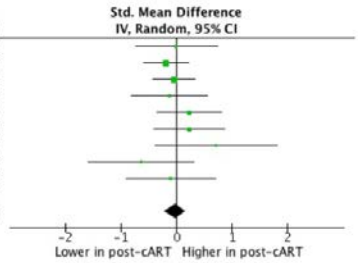
B

Frontal White Matter

NAA

Study or Subgroup	Post-cART Mean	SD	Total	Pre-cART Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 1999	7.56	12.43	14	7.62	0.51	14	7.0%	-0.01 [-0.75, 0.73]
Mora-Peris: 2018	1.23	0.22	46	1.27	0.2	46	23.0%	-0.19 [-0.60, 0.22]
Sailasuta 2016	11.72	1.29	50	11.77	1.16	59	27.2%	-0.04 [-0.42, 0.34]
Tarasow 2004	1.8	0.35	14	1.84	0.29	20	8.3%	-0.12 [-0.81, 0.56]
Valcour cART 2015	11.97	1.11	22	11.66	1.48	24	11.5%	0.23 [-0.35, 0.81]
Valcour cART+ 2015	12.43	1.23	18	12.15	1.11	20	9.5%	0.23 [-0.40, 0.87]
Winston Arm 1 2010	2.48	1.12	7	1.86	0.28	7	3.2%	0.71 [-0.38, 1.80]
Winston Arm 2 2010	1.68	0.17	9	1.83	0.27	9	4.3%	-0.63 [-1.59, 0.32]
Winston Arm 3 2010	1.86	0.65	12	1.92	0.44	12	6.0%	-0.10 [-0.91, 0.70]
Total (95% CI)			**192**			**211**	**100.0%**	**-0.03 [-0.22, 0.17]**

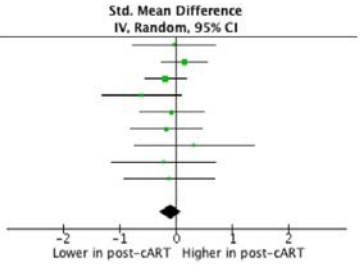
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.43$, df = 8 (P = 0.71); $I^2 = 0\%$
Test for overall effect: Z = 0.27 (P = 0.79)



Cho

Study or Subgroup	Post-cART Mean	SD	Total	Pre-cART Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 1999	1.84	0.28	14	1.85	0.23	14	7.0%	-0.04 [-0.78, 0.70]
Mora-Peris: 2018	0.32	0.07	46	0.31	0.06	46	23.0%	0.15 [-0.26, 0.56]
Sailasuta 2016	2.9	0.37	50	2.97	0.38	59	27.1%	-0.19 [-0.56, 0.19]
Tarasow 2004	0.84	0.31	14	1.01	0.24	20	7.9%	-0.61 [-1.31, 0.09]
Valcour cART 2015	2.85	0.37	22	2.88	0.4	24	11.5%	-0.08 [-0.66, 0.50]
Valcour cART+ 2015	2.87	0.26	18	2.93	0.39	20	9.5%	-0.18 [-0.81, 0.46]
Winston Arm 1 2010	1.17	0.18	7	1.11	0.17	7	3.5%	0.32 [-0.74, 1.38]
Winston Arm 2 2010	1.11	0.13	9	1.16	0.28	9	4.5%	-0.22 [-1.15, 0.71]
Winston Arm 3 2010	1.2	0.2	12	1.24	0.4	12	6.0%	-0.12 [-0.92, 0.68]
Total (95% CI)			**192**			**211**	**100.0%**	**-0.10 [-0.29, 0.10]**

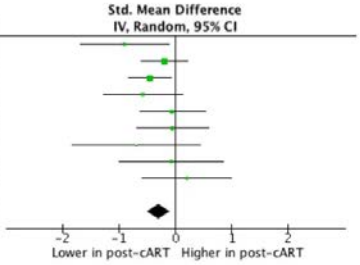
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.48$, df = 8 (P = 0.81); $I^2 = 0\%$
Test for overall effect: Z = 0.97 (P = 0.33)



mI

Study or Subgroup	Post-cART Mean	SD	Total	Pre-cART Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 1999	7.83	1.14	14	8.84	1.05	14	6.4%	-0.89 [-1.68, -0.11]
Mora-Peris: 2018	0.7	0.21	46	0.74	0.2	46	23.4%	-0.19 [-0.60, 0.22]
Sailasuta 2016	8.19	1.16	50	8.91	1.87	59	27.0%	-0.45 [-0.83, -0.07]
Tarasow 2004	0.63	0.26	14	0.78	0.25	20	8.1%	-0.58 [-1.27, 0.12]
Valcour cART 2015	8.17	1.85	22	8.26	1.54	24	11.7%	-0.05 [-0.63, 0.53]
Valcour cART+ 2015	7.77	1.32	18	7.85	1.65	20	9.7%	-0.05 [-0.69, 0.58]
Winston Arm 1 2010	2.6	1.58	6	3.85	1.76	7	3.0%	-0.69 [-1.83, 0.44]
Winston Arm 2 2010	3.73	0.77	9	3.8	1.09	9	4.6%	-0.07 [-0.99, 0.85]
Winston Arm 3 2010	4.26	1.6	12	3.88	1.99	12	6.1%	0.20 [-0.60, 1.01]
Total (95% CI)			**191**			**211**	**100.0%**	**-0.29 [-0.49, -0.10]**

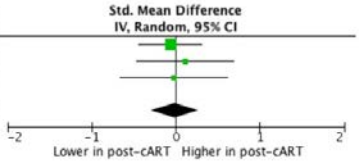
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.17$, df = 8 (P = 0.52); $I^2 = 0\%$
Test for overall effect: Z = 2.91 (P = 0.004)



Glx

Study or Subgroup	Post-cART Mean	SD	Total	Pre-cART Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Sailasuta 2016	10.26	1.98	50	10.38	1.76	59	56.4%	-0.06 [-0.44, 0.31]
Valcour cART 2015	13.84	2.2	22	13.59	2.1	24	23.9%	0.11 [-0.46, 0.69]
Valcour cART+ 2015	14.52	2.33	18	14.58	2.77	20	19.7%	-0.02 [-0.66, 0.61]
Total (95% CI)			**90**			**103**	**100.0%**	**-0.01 [-0.30, 0.27]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.26$, df = 2 (P = 0.88); $I^2 = 0\%$
Test for overall effect: Z = 0.09 (P = 0.93)



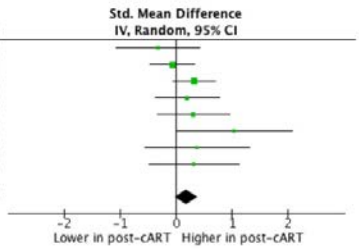
C

Frontal Gray Matter

NAA

Study or Subgroup	Post-cART Mean	SD	Total	Pre-cART Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 1999	8.59	1	14	8.86	0.6	14	7.4%	-0.32 [-1.06, 0.43]
Mora-Peris 2018	1.1	0.16	48	1.11	0.16	48	25.9%	-0.06 [-0.46, 0.34]
Sailasuta 2016	9.39	0.86	50	9.04	1.21	59	28.8%	0.33 [-0.05, 0.71]
Valcour cART 2015	8.91	1.57	24	8.62	1.23	24	12.9%	0.20 [-0.37, 0.77]
Valcour cART+ 2015	9.11	1.03	18	8.74	1.27	20	10.1%	0.31 [-0.33, 0.95]
Winston Arm 1 2010	1.92	0.36	9	1.56	0.29	8	3.9%	1.04 [0.01, 2.07]
Winston Arm 2 2010	1.81	0.95	9	1.54	0.17	9	4.7%	0.38 [-0.56, 1.31]
Winston Arm 3 2010	1.74	0.31	12	1.64	0.29	12	6.4%	0.32 [-0.48, 1.13]
Total (95% CI)			**184**			**194**	**100.0%**	**0.19 [-0.01, 0.39]**

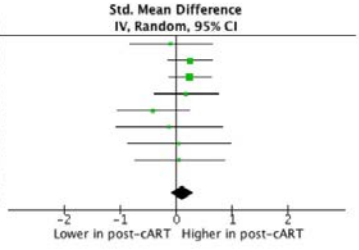
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.79$, df = 7 (P = 0.45); $I^2 = 0\%$
Test for overall effect: Z = 1.83 (P = 0.07)



Cho

Study or Subgroup	Post-cART Mean	SD	Total	Pre-cART Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 1999	2.31	0.6	14	2.36	0.36	14	7.5%	-0.10 [-0.84, 0.64]
Mora-Peris 2018	0.22	0.04	48	0.21	0.04	48	25.4%	0.25 [-0.15, 0.65]
Sailasuta 2016	2.11	0.32	50	2.04	0.25	59	28.7%	0.24 [-0.13, 0.62]
Valcour cART 2015	2.06	0.3	24	2.01	0.24	24	12.8%	0.18 [-0.39, 0.75]
Valcour cART+ 2015	1.91	0.2	18	2.01	0.27	20	9.9%	-0.41 [-1.05, 0.24]
Winston Arm 1 2010	0.69	0.16	9	0.71	0.15	8	4.5%	-0.12 [-1.08, 0.83]
Winston Arm 2 2010	0.72	0.17	9	0.71	0.18	9	4.8%	0.05 [-0.87, 0.98]
Winston Arm 3 2010	0.67	0.15	12	0.66	0.14	12	6.4%	0.07 [-0.73, 0.87]
Total (95% CI)			**184**			**194**	**100.0%**	**0.11 [-0.09, 0.31]**

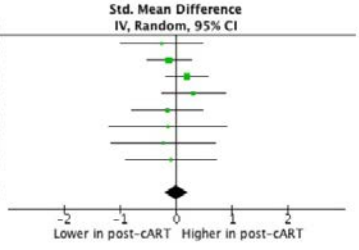
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.05$, df = 7 (P = 0.77); $I^2 = 0\%$
Test for overall effect: Z = 1.06 (P = 0.29)



mI

Study or Subgroup	Post-cART Mean	SD	Total	Pre-cART Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 1999	8.6	1.68	14	9	1.31	14	7.5%	-0.26 [-1.00, 0.49]
Mora-Peris 2018	0.64	0.15	48	0.66	0.17	48	25.8%	-0.12 [-0.52, 0.28]
Sailasuta 2016	6.85	0.84	50	6.68	0.86	59	29.0%	0.20 [-0.18, 0.58]
Valcour cART 2015	6.52	1.07	24	6.19	0.98	24	12.8%	0.32 [-0.25, 0.89]
Valcour cART+ 2015	6.21	0.84	18	6.34	0.84	20	10.2%	-0.15 [-0.79, 0.49]
Winston Arm 1 2010	3	1.66	8	3.27	1.8	6	3.7%	-0.15 [-1.21, 0.91]
Winston Arm 2 2010	2.97	1.42	9	3.25	0.86	9	4.8%	-0.23 [-1.15, 0.70]
Winston Arm 3 2010	2.65	1.4	11	2.77	1.02	12	6.2%	-0.10 [-0.91, 0.72]
Total (95% CI)			**182**			**192**	**100.0%**	**0.01 [-0.19, 0.21]**

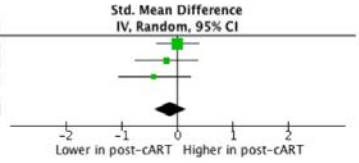
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.64$, df = 7 (P = 0.82); $I^2 = 0\%$
Test for overall effect: Z = 0.09 (P = 0.93)



Glx

Study or Subgroup	Post-cART Mean	SD	Total	Pre-cART Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Sailasuta 2016	11.56	2.01	50	11.55	1.96	59	56.1%	0.01 [-0.37, 0.38]
Valcour cART 2015	16.09	2.27	24	16.56	2.56	24	24.7%	-0.19 [-0.76, 0.38]
Valcour cART+ 2015	15.89	2.48	18	16.79	1.77	20	19.2%	-0.41 [-1.06, 0.23]
Total (95% CI)			**92**			**103**	**100.0%**	**-0.12 [-0.41, 0.16]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.28$, df = 2 (P = 0.53); $I^2 = 0\%$
Test for overall effect: Z = 0.86 (P = 0.39)



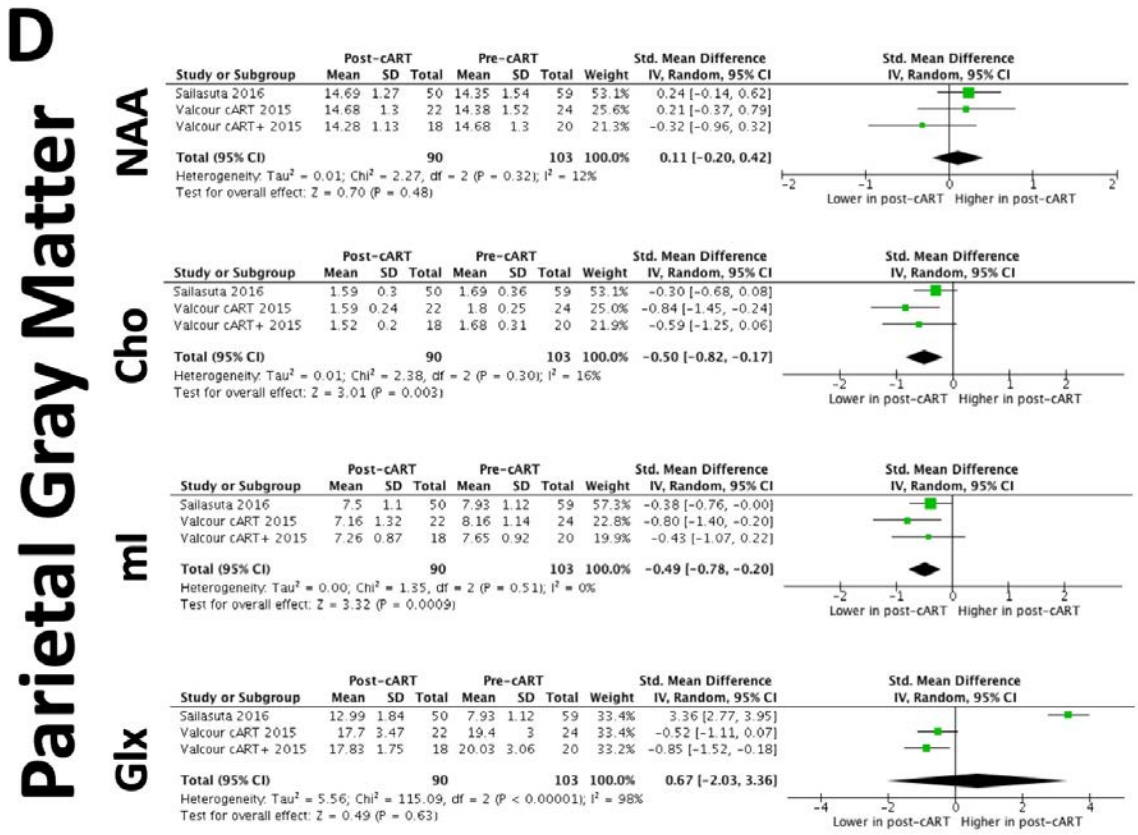
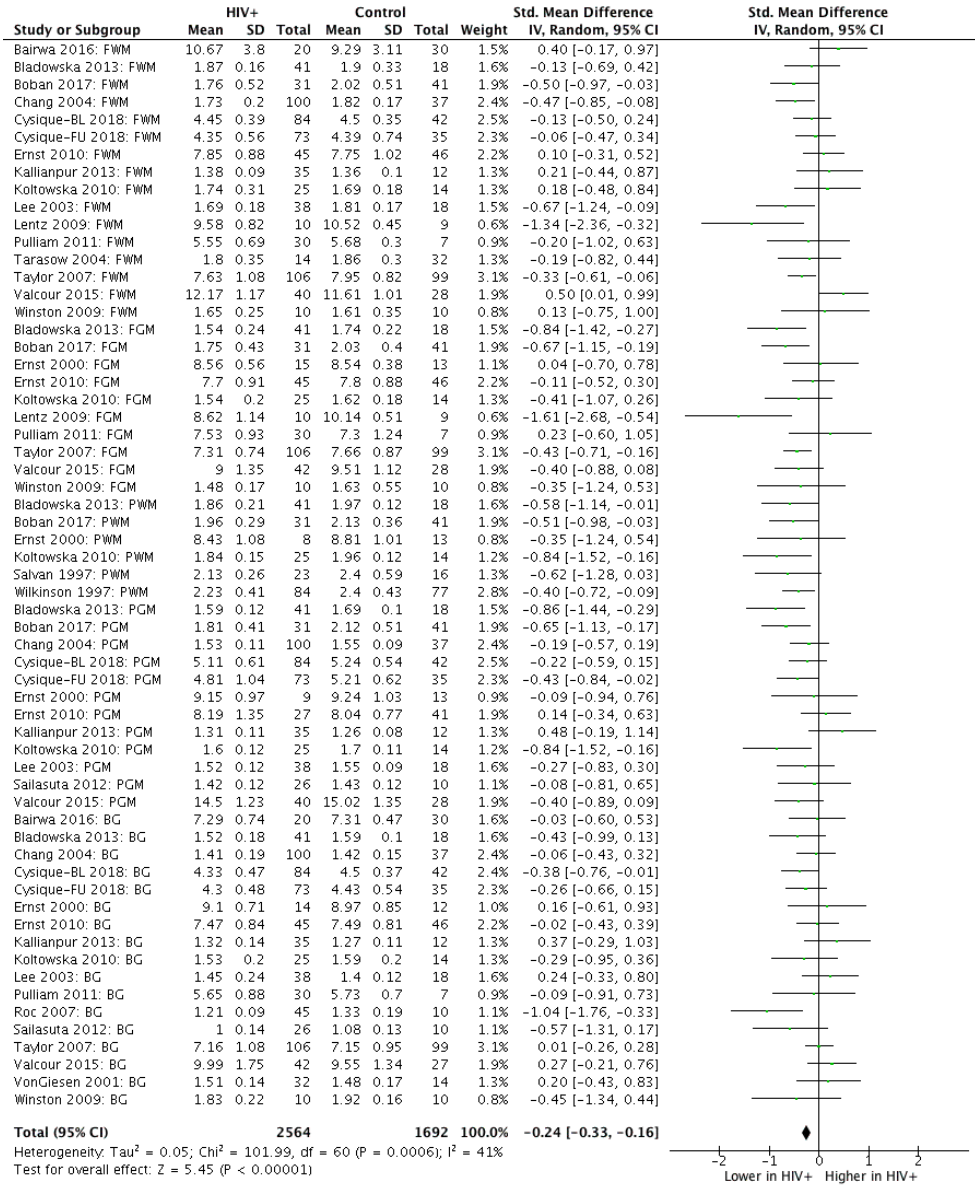


Figure e-4. Study effect sizes of brain metabolites between after and before cART in cART-naïve PWH in the primary meta-analysis

(**A**) Basal Ganglia; (**B**) Frontal White Matter; (**C**) Frontal Gray Matter; (**D**) Parietal Gray Matter. Metabolites: NAA, N-acetyl aspartate; Cho, choline; mI, myo-Inositol; Glx, glutamate (Glu), or a combination of Glu and glutamine (Gln). Groups: pre-cART, before cART; post-cART, approximately 6-12 months after cART (with the same group of subjects).

A

NAA

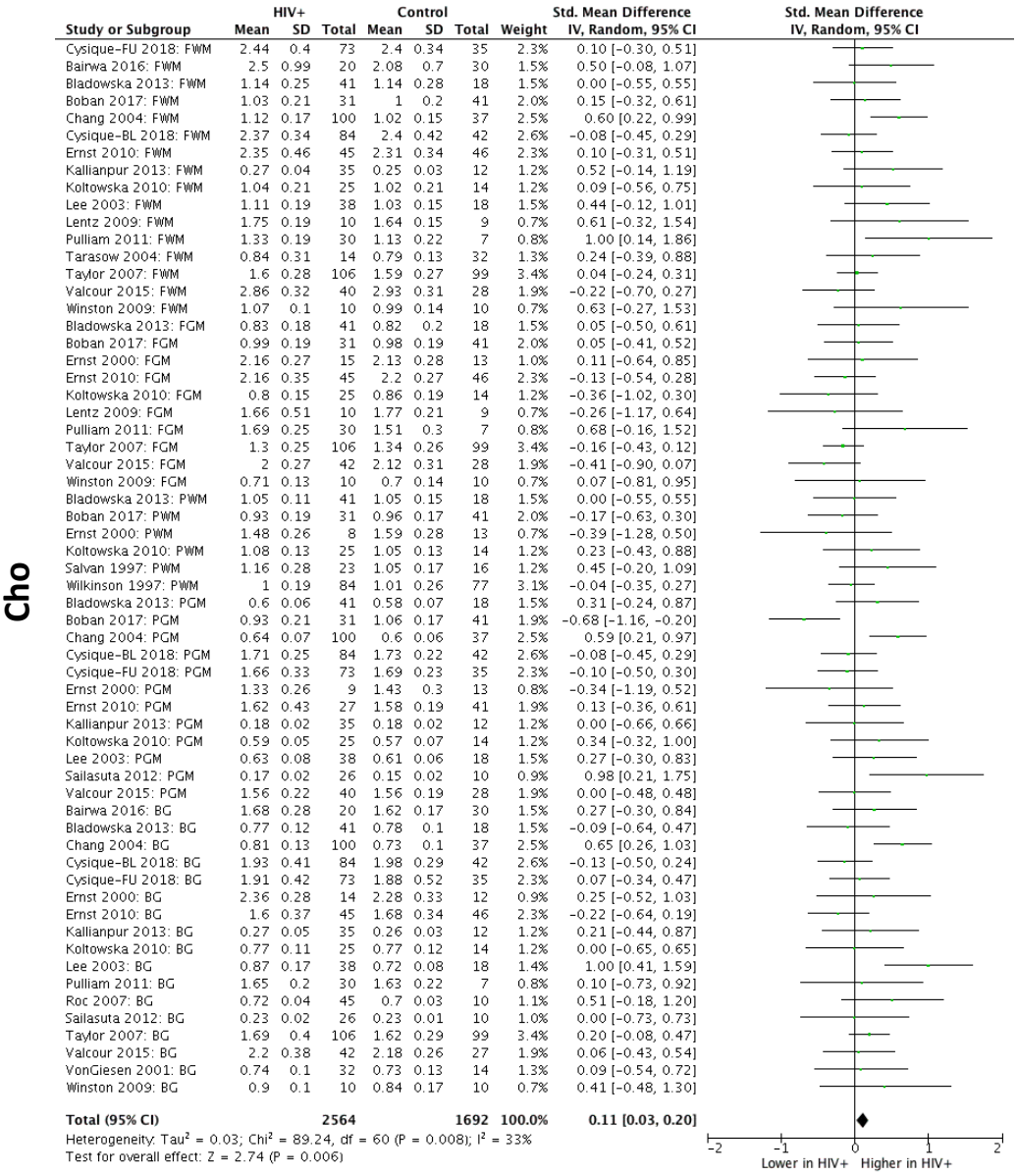


Study or Subgroup	HIV+ Mean	HIV+ SD	HIV+ Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bairwa 2016: FWM	10.67	3.8	20	9.29	3.11	30	1.5%	0.40 [-0.17, 0.97]
Bladowska 2013: FWM	1.87	0.16	41	1.9	0.33	18	1.6%	-0.13 [-0.69, 0.42]
Boban 2017: FWM	1.76	0.52	31	2.02	0.51	41	1.9%	-0.50 [-0.97, -0.03]
Chang 2004: FWM	1.73	0.2	100	1.82	0.17	37	2.4%	-0.47 [-0.85, -0.08]
Cysique-BL 2018: FWM	4.45	0.39	84	4.5	0.35	42	2.5%	-0.13 [-0.50, 0.24]
Cysique-FU 2018: FWM	4.35	0.56	73	4.39	0.74	35	2.3%	-0.06 [-0.47, 0.34]
Ernst 2010: FWM	7.85	0.88	45	7.75	1.02	46	2.2%	0.10 [-0.31, 0.52]
Kallianpur 2013: FWM	1.38	0.09	35	1.36	0.1	12	1.3%	0.21 [-0.44, 0.87]
Koltowska 2010: FWM	1.74	0.31	25	1.69	0.18	14	1.3%	0.18 [-0.48, 0.84]
Lee 2003: FWM	1.69	0.18	38	1.81	0.17	18	1.5%	-0.67 [-1.24, -0.09]
Lentz 2009: FWM	9.58	0.82	10	10.52	0.45	9	0.6%	-1.34 [-2.36, -0.32]
Pulliam 2011: FWM	5.55	0.69	30	5.68	0.3	7	0.9%	-0.20 [-1.02, 0.63]
Tarasow 2004: FWM	1.8	0.35	14	1.86	0.3	32	1.3%	-0.19 [-0.82, 0.44]
Taylor 2007: FWM	7.63	1.08	106	7.95	0.82	99	3.1%	-0.33 [-0.61, -0.06]
Valcour 2015: FWM	12.17	1.17	40	11.61	1.01	28	1.9%	0.50 [0.01, 0.99]
Winston 2009: FWM	1.65	0.25	10	1.61	0.35	10	0.8%	0.13 [-0.75, 1.00]
Bladowska 2013: FGM	1.54	0.24	41	1.74	0.22	18	1.5%	-0.84 [-1.42, -0.27]
Boban 2017: FGM	1.75	0.43	31	2.03	0.4	41	1.9%	-0.67 [-1.15, -0.19]
Ernst 2000: FGM	8.56	0.56	15	8.54	0.38	13	1.1%	0.04 [-0.70, 0.78]
Ernst 2010: FGM	7.7	0.91	45	7.8	0.88	46	2.2%	-0.11 [-0.52, 0.30]
Koltowska 2010: FGM	1.54	0.2	25	1.62	0.18	14	1.3%	-0.41 [-1.07, 0.26]
Lentz 2009: FGM	8.62	1.14	10	10.14	0.51	9	0.6%	-1.61 [-2.68, -0.54]
Pulliam 2011: FGM	7.53	0.93	30	7.3	1.24	7	0.9%	0.23 [-0.60, 1.05]
Taylor 2007: FGM	7.31	0.74	106	7.66	0.87	99	3.1%	-0.43 [-0.71, -0.16]
Valcour 2015: FGM	9	1.35	42	9.51	1.12	28	1.9%	-0.40 [-0.88, 0.08]
Winston 2009: FGM	1.48	0.17	10	1.63	0.55	10	0.8%	-0.35 [-1.24, 0.53]
Bladowska 2013: PWM	1.86	0.21	41	1.97	0.12	18	1.6%	-0.58 [-1.14, -0.01]
Boban 2017: PWM	1.96	0.29	31	2.13	0.36	41	1.9%	-0.51 [-0.98, -0.03]
Ernst 2000: PWM	8.43	1.08	8	8.81	1.01	13	0.8%	-0.35 [-1.24, 0.54]
Koltowska 2010: PWM	1.84	0.15	25	1.96	0.12	14	1.2%	-0.84 [-1.52, -0.16]
Salvan 1997: PWM	2.13	0.26	23	2.4	0.59	16	1.3%	-0.62 [-1.28, 0.03]
Wilkinson 1997: PWM	2.23	0.41	84	2.4	0.43	77	2.8%	-0.40 [-0.72, -0.09]
Bladowska 2013: PGM	1.59	0.12	41	1.69	0.1	18	1.5%	-0.86 [-1.44, -0.29]
Boban 2017: PGM	1.81	0.41	31	2.12	0.51	41	1.9%	-0.65 [-1.13, -0.17]
Chang 2004: PGM	1.53	0.11	100	1.55	0.09	37	2.4%	-0.19 [-0.57, 0.19]
Cysique-BL 2018: PGM	5.11	0.61	84	5.24	0.54	42	2.5%	-0.22 [-0.59, 0.15]
Cysique-FU 2018: PGM	4.81	1.04	73	5.21	0.62	35	2.3%	-0.43 [-0.84, -0.02]
Ernst 2000: PGM	9.15	0.97	9	9.24	1.03	13	0.9%	-0.09 [-0.94, 0.76]
Ernst 2010: PGM	8.19	1.35	27	8.04	0.77	41	1.9%	0.14 [-0.34, 0.63]
Kallianpur 2013: PGM	1.31	0.11	35	1.26	0.08	12	1.3%	0.48 [-0.19, 1.14]
Koltowska 2010: PGM	1.6	0.12	25	1.7	0.11	14	1.2%	-0.84 [-1.52, -0.16]
Lee 2003: PGM	1.52	0.12	38	1.55	0.09	18	1.6%	-0.27 [-0.83, 0.30]
Sailasuta 2012: PGM	1.42	0.12	26	1.43	0.12	10	1.1%	-0.08 [-0.81, 0.65]
Valcour 2015: PGM	14.5	1.23	40	15.02	1.35	28	1.9%	-0.40 [-0.89, 0.09]
Bairwa 2016: BG	7.29	0.74	20	7.31	0.47	30	1.6%	-0.03 [-0.60, 0.53]
Bladowska 2013: BG	1.52	0.18	41	1.59	0.1	18	1.6%	-0.43 [-0.99, 0.13]
Chang 2004: BG	1.41	0.19	100	1.42	0.15	37	2.4%	-0.06 [-0.43, 0.32]
Cysique-BL 2018: BG	4.33	0.47	84	4.5	0.37	42	2.4%	-0.38 [-0.76, -0.01]
Cysique-FU 2018: BG	4.3	0.48	73	4.43	0.54	35	2.3%	-0.26 [-0.66, 0.15]
Ernst 2000: BG	9.1	0.71	14	8.97	0.85	12	1.0%	0.16 [-0.61, 0.93]
Ernst 2010: BG	7.47	0.84	45	7.49	0.81	46	2.2%	-0.02 [-0.43, 0.39]
Kallianpur 2013: BG	1.32	0.14	35	1.27	0.11	12	1.3%	0.37 [-0.29, 1.03]
Koltowska 2010: BG	1.53	0.2	25	1.59	0.2	14	1.3%	-0.29 [-0.95, 0.36]
Lee 2003: BG	1.45	0.24	38	1.4	0.12	18	1.6%	0.24 [-0.33, 0.80]
Pulliam 2011: BG	5.65	0.88	30	5.73	0.7	7	0.9%	-0.09 [-0.91, 0.73]
Roc 2007: BG	1.21	0.09	45	1.33	0.19	10	1.1%	-1.04 [-1.76, -0.33]
Sailasuta 2012: BG	1	0.14	26	1.08	0.13	10	1.1%	-0.57 [-1.31, 0.17]
Taylor 2007: BG	7.16	1.08	106	7.15	0.95	99	3.1%	0.01 [-0.26, 0.28]
Valcour 2015: BG	9.99	1.75	42	9.55	1.34	27	1.9%	0.27 [-0.21, 0.76]
VonGiesen 2001: BG	1.51	0.14	32	1.48	0.17	14	1.3%	0.20 [-0.43, 0.83]
Winston 2009: BG	1.83	0.22	10	1.92	0.16	10	0.8%	-0.45 [-1.34, 0.44]
Total (95% CI)			**2564**			**1692**	**100.0%**	**-0.24 [-0.33, -0.16]**

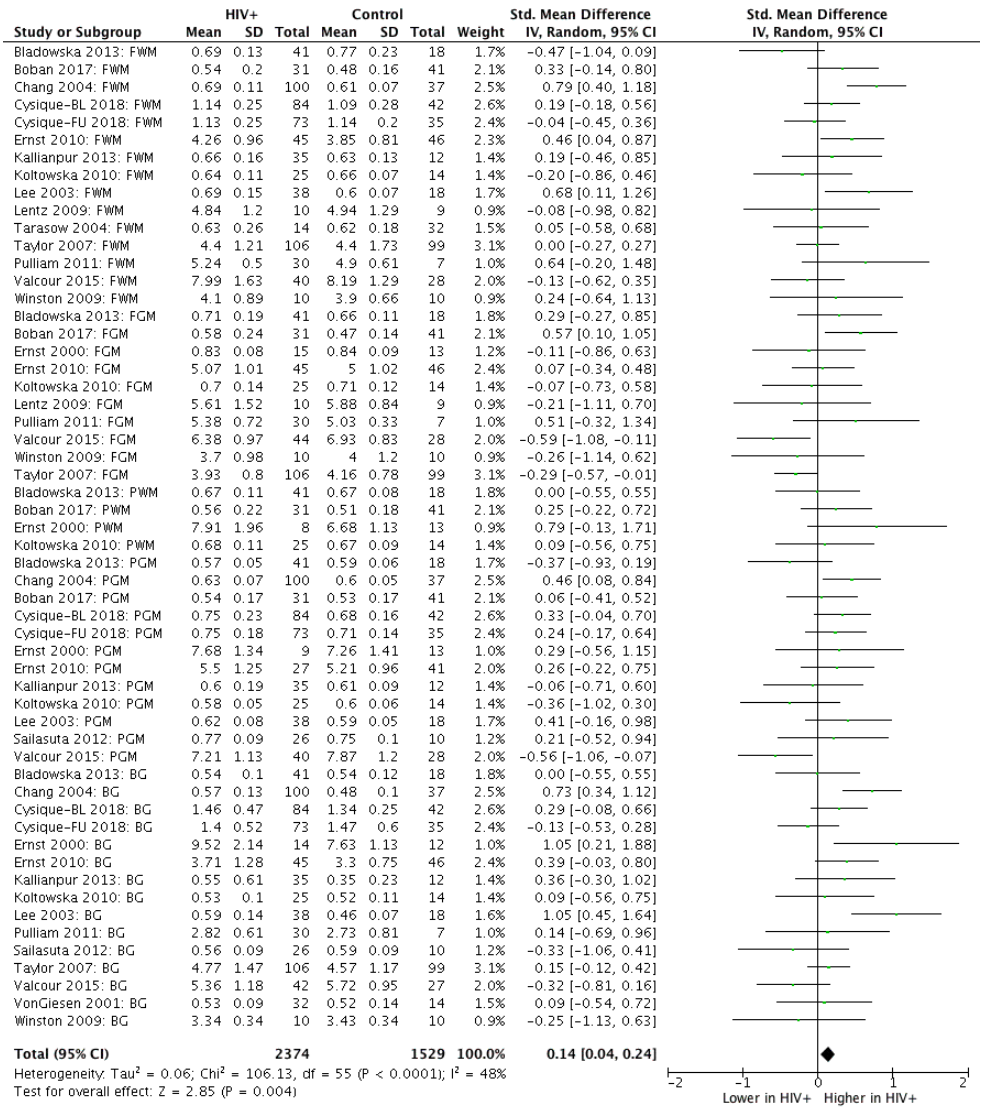
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 101.99$, df = 60 (P = 0.0006); $I^2 = 41\%$

Test for overall effect: Z = 5.45 (P < 0.00001)

Cho


HIV+
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Cysique-FU 2018: FWM 2.44 0.4 73 2.4 0.34 35 2.3% 0.10 [-0.30, 0.51]
Bairwa 2016: FWM 2.5 0.99 20 2.08 0.7 30 1.5% 0.50 [-0.08, 1.07]
Bladowska 2013: FWM 1.14 0.25 41 1.14 0.28 18 1.5% 0.00 [-0.55, 0.55]
Boban 2017: FWM 1.03 0.21 31 1 0.2 41 2.0% 0.15 [-0.32, 0.61]
Chang 2004: FWM 1.12 0.17 100 1.02 0.15 37 2.5% 0.60 [0.22, 0.99]
Cysique-BL 2018: FWM 2.37 0.34 84 2.4 0.42 42 2.6% -0.08 [-0.45, 0.29]
Ernst 2010: FWM 2.35 0.46 45 2.31 0.34 46 2.3% 0.10 [-0.31, 0.51]
Kallianpur 2013: FWM 0.27 0.04 35 0.25 0.03 12 1.2% 0.52 [-0.14, 1.19]
Koltowska 2010: FWM 1.04 0.21 25 1.02 0.21 14 1.2% 0.09 [-0.56, 0.75]
Lee 2003: FWM 1.11 0.19 38 1.03 0.15 18 1.5% 0.44 [-0.12, 1.01]
Lentz 2009: FWM 1.75 0.19 10 1.64 0.15 9 0.7% 0.61 [-0.32, 1.54]
Pulliam 2011: FWM 1.33 0.19 30 1.13 0.22 7 0.8% 1.00 [0.14, 1.86]
Tarasow 2004: FWM 0.84 0.31 14 0.79 0.13 32 1.3% 0.24 [-0.39, 0.88]
Taylor 2007: FWM 1.6 0.28 106 1.59 0.27 99 3.4% 0.04 [-0.24, 0.31]
Valcour 2015: FWM 2.86 0.32 40 2.93 0.31 28 1.9% -0.22 [-0.70, 0.27]
Winston 2009: FWM 1.07 0.1 10 0.99 0.14 10 0.7% 0.63 [-0.27, 1.53]
Bladowska 2013: FGM 0.83 0.18 41 0.82 0.2 18 1.5% 0.05 [-0.50, 0.61]
Boban 2017: FGM 0.99 0.19 31 0.98 0.19 41 2.0% 0.05 [-0.41, 0.52]
Ernst 2000: FGM 2.16 0.27 15 2.13 0.28 13 1.0% 0.11 [-0.64, 0.85]
Ernst 2010: FGM 2.16 0.35 45 2.2 0.27 46 2.3% -0.13 [-0.54, 0.28]
Koltowska 2010: FGM 0.8 0.15 25 0.86 0.19 14 1.2% -0.36 [-1.02, 0.30]
Lentz 2009: FGM 1.66 0.51 10 1.77 0.21 9 0.7% -0.26 [-1.17, 0.64]
Pulliam 2011: FGM 1.69 0.25 30 1.51 0.3 7 0.8% 0.68 [-0.16, 1.52]
Taylor 2007: FGM 1.3 0.25 106 1.34 0.26 99 3.4% -0.16 [-0.43, 0.12]
Valcour 2015: FGM 2 0.27 42 2.12 0.31 28 1.9% -0.41 [-0.90, 0.07]
Winston 2009: FGM 0.71 0.13 10 0.7 0.14 10 0.7% 0.07 [-0.81, 0.95]
Bladowska 2013: PWM 1.05 0.11 41 1.05 0.15 18 1.5% 0.00 [-0.55, 0.55]
Boban 2017: PWM 0.93 0.19 31 0.96 0.17 41 2.0% -0.17 [-0.63, 0.30]
Ernst 2000: PWM 1.48 0.26 8 1.59 0.28 13 0.7% -0.39 [-1.28, 0.50]
Koltowska 2010: PWM 1.08 0.13 25 1.05 0.13 14 1.2% 0.23 [-0.43, 0.88]
Salvan 1997: PWM 1.16 0.28 23 1.05 0.17 16 1.2% 0.45 [-0.20, 1.09]
Wilkinson 1997: PWM 1 0.19 84 1.01 0.26 77 3.1% -0.04 [-0.35, 0.27]
Bladowska 2013: PGM 0.6 0.06 41 0.58 0.07 18 1.5% 0.31 [-0.24, 0.87]
Boban 2017: PGM 0.93 0.21 31 1.06 0.17 41 1.9% -0.68 [-1.16, -0.20]
Chang 2004: PGM 0.64 0.07 100 0.6 0.06 37 2.5% 0.59 [0.21, 0.97]
Cysique-BL 2018: PGM 1.71 0.25 84 1.73 0.22 42 2.6% -0.08 [-0.45, 0.29]
Cysique-FU 2018: PGM 1.66 0.33 73 1.69 0.23 35 2.3% -0.10 [-0.50, 0.30]
Ernst 2000: PGM 1.33 0.26 9 1.43 0.3 13 0.8% -0.34 [-1.19, 0.52]
Ernst 2010: PGM 1.62 0.43 27 1.58 0.19 41 1.9% 0.13 [-0.36, 0.61]
Kallianpur 2013: PGM 0.18 0.02 35 0.18 0.02 12 1.2% 0.00 [-0.66, 0.66]
Koltowska 2010: PGM 0.59 0.05 25 0.57 0.07 14 1.2% 0.34 [-0.32, 1.00]
Lee 2003: PGM 0.63 0.08 38 0.61 0.06 18 1.5% 0.27 [-0.30, 0.83]
Sailasuta 2012: PGM 0.17 0.02 26 0.15 0.02 10 0.9% 0.98 [0.21, 1.75]
Valcour 2015: PGM 1.56 0.22 40 1.56 0.19 28 1.9% 0.00 [-0.48, 0.48]
Bairwa 2016: BG 1.68 0.28 20 1.62 0.17 30 1.5% 0.27 [-0.30, 0.84]
Bladowska 2013: BG 0.77 0.12 41 0.78 0.1 18 1.5% -0.09 [-0.64, 0.47]
Chang 2004: BG 0.81 0.13 100 0.73 0.1 37 2.5% 0.65 [0.26, 1.03]
Cysique-BL 2018: BG 1.93 0.41 84 1.98 0.29 42 2.6% -0.13 [-0.50, 0.24]
Cysique-FU 2018: BG 1.91 0.42 73 1.88 0.52 35 2.3% 0.07 [-0.34, 0.47]
Ernst 2000: BG 2.36 0.28 14 2.28 0.33 12 0.9% 0.25 [-0.52, 1.03]
Ernst 2010: BG 1.6 0.37 45 1.68 0.34 46 2.3% -0.22 [-0.64, 0.19]
Kallianpur 2013: BG 0.27 0.05 35 0.26 0.03 12 1.2% 0.21 [-0.44, 0.87]
Koltowska 2010: BG 0.77 0.11 25 0.77 0.12 14 1.2% 0.00 [-0.65, 0.65]
Lee 2003: BG 0.87 0.17 38 0.72 0.08 18 1.4% 1.00 [0.41, 1.59]
Pulliam 2011: BG 1.65 0.2 30 1.63 0.22 7 0.8% 0.10 [-0.73, 0.92]
Roc 2007: BG 0.72 0.04 45 0.7 0.03 10 1.1% 0.51 [-0.18, 1.20]
Sailasuta 2012: BG 0.23 0.02 26 0.23 0.01 10 1.0% 0.00 [-0.73, 0.73]
Taylor 2007: BG 1.69 0.4 106 1.62 0.29 99 3.4% 0.20 [-0.08, 0.47]
Valcour 2015: BG 2.2 0.38 42 2.18 0.26 27 1.9% 0.06 [-0.43, 0.54]
VonGiesen 2001: BG 0.74 0.1 32 0.73 0.13 14 1.3% 0.09 [-0.54, 0.72]
Winston 2009: BG 0.9 0.1 10 0.84 0.17 10 0.7% 0.41 [-0.48, 1.30]
Total (95% CI) 2564 1692 100.0% 0.11 [0.03, 0.20]
Heterogeneity: Tau² = 0.03; Chi² = 89.24, df = 60 (P = 0.008); I² = 33%
Test for overall effect: Z = 2.74 (P = 0.006)
-2 -1 0 1 2
Lower in HIV+ Higher in HIV+

ml



Study or Subgroup	HIV+ Mean	HIV+ SD	HIV+ Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bladowska 2013: FWM	0.69	0.13	41	0.77	0.23	18	1.7%	−0.47 [−1.04, 0.09]
Boban 2017: FWM	0.54	0.2	31	0.48	0.16	41	2.1%	0.33 [−0.14, 0.80]
Chang 2004: FWM	0.69	0.11	100	0.61	0.07	37	2.5%	0.79 [0.40, 1.18]
Cysique-BL 2018: FWM	1.14	0.25	84	1.09	0.28	42	2.6%	0.19 [−0.18, 0.56]
Cysique-FU 2018: FWM	1.13	0.25	73	1.14	0.2	35	2.4%	−0.04 [−0.45, 0.36]
Ernst 2010: FWM	4.26	0.96	45	3.85	0.81	46	2.3%	0.46 [0.04, 0.87]
Kallianpur 2013: FWM	0.66	0.16	35	0.63	0.13	12	1.4%	0.19 [−0.46, 0.85]
Koltowska 2010: FWM	0.64	0.11	25	0.66	0.07	14	1.4%	−0.20 [−0.86, 0.46]
Lee 2003: FWM	0.69	0.15	38	0.6	0.07	18	1.7%	0.68 [0.11, 1.26]
Lentz 2009: FWM	4.84	1.2	10	4.94	1.29	9	0.9%	−0.08 [−0.98, 0.82]
Tarasow 2004: FWM	0.63	0.26	14	0.62	0.18	32	1.5%	0.05 [−0.58, 0.68]
Taylor 2007: FWM	4.4	1.21	106	4.4	1.73	99	3.1%	0.00 [−0.27, 0.27]
Pulliam 2011: FWM	5.24	0.5	30	4.9	0.61	7	1.0%	0.64 [−0.20, 1.48]
Valcour 2015: FWM	7.99	1.63	40	8.19	1.29	28	2.0%	−0.13 [−0.62, 0.35]
Winston 2009: FWM	4.1	0.89	10	3.9	0.66	10	0.9%	0.24 [−0.64, 1.13]
Bladowska 2013: FGM	0.71	0.19	41	0.66	0.11	18	1.8%	0.29 [−0.27, 0.85]
Boban 2017: FGM	0.58	0.24	31	0.47	0.14	41	2.1%	0.57 [0.10, 1.05]
Ernst 2000: FGM	0.83	0.08	15	0.84	0.09	13	1.2%	−0.11 [−0.86, 0.63]
Ernst 2010: FGM	5.07	1.01	45	5	1.02	46	2.4%	0.07 [−0.34, 0.48]
Koltowska 2010: FGM	0.7	0.14	25	0.71	0.12	14	1.4%	−0.07 [−0.73, 0.58]
Lentz 2009: FGM	5.61	1.52	10	5.88	0.84	9	0.9%	−0.21 [−1.11, 0.70]
Pulliam 2011: FGM	5.38	0.72	30	5.03	0.33	7	1.0%	0.51 [−0.32, 1.34]
Valcour 2015: FGM	6.38	0.97	44	6.93	0.83	28	2.0%	−0.59 [−1.08, −0.11]
Winston 2009: FGM	3.7	0.98	10	4	1.2	10	0.9%	−0.26 [−1.14, 0.62]
Taylor 2007: FGM	3.93	0.8	106	4.16	0.78	99	3.1%	−0.29 [−0.57, −0.01]
Bladowska 2013: PWM	0.67	0.11	41	0.67	0.08	18	1.8%	0.00 [−0.55, 0.55]
Boban 2017: PWM	0.56	0.22	31	0.51	0.18	41	2.1%	0.25 [−0.22, 0.72]
Ernst 2000: PWM	7.91	1.96	8	6.68	1.13	13	0.9%	0.79 [−0.13, 1.71]
Koltowska 2010: PWM	0.68	0.11	25	0.67	0.09	14	1.4%	0.09 [−0.56, 0.75]
Bladowska 2013: PGM	0.57	0.05	41	0.59	0.06	18	1.7%	−0.37 [−0.93, 0.19]
Chang 2004: PGM	0.63	0.07	100	0.6	0.05	37	2.5%	0.46 [0.08, 0.84]
Boban 2017: PGM	0.54	0.17	31	0.53	0.17	41	2.1%	0.06 [−0.41, 0.52]
Cysique-BL 2018: PGM	0.75	0.23	84	0.68	0.16	42	2.6%	0.33 [−0.04, 0.70]
Cysique-FU 2018: PGM	0.75	0.18	73	0.71	0.14	35	2.4%	0.24 [−0.17, 0.64]
Ernst 2000: PGM	7.68	1.34	9	7.26	1.41	13	1.0%	0.29 [−0.56, 1.15]
Ernst 2010: PGM	5.5	1.25	27	5.21	0.96	41	2.0%	0.26 [−0.22, 0.75]
Kallianpur 2013: PGM	0.6	0.19	35	0.61	0.09	12	1.4%	−0.06 [−0.71, 0.60]
Koltowska 2010: PGM	0.58	0.05	25	0.6	0.06	14	1.4%	−0.36 [−1.02, 0.30]
Lee 2003: PGM	0.62	0.08	38	0.59	0.05	18	1.7%	0.41 [−0.16, 0.98]
Sailasuta 2012: PGM	0.77	0.09	26	0.75	0.1	10	1.2%	0.21 [−0.52, 0.94]
Valcour 2015: PGM	7.21	1.13	40	7.87	1.2	28	2.0%	−0.56 [−1.06, −0.07]
Bladowska 2013: BG	0.54	0.1	41	0.54	0.12	18	1.8%	0.00 [−0.55, 0.55]
Chang 2004: BG	0.57	0.13	100	0.48	0.1	37	2.5%	0.73 [0.34, 1.12]
Cysique-BL 2018: BG	1.46	0.47	84	1.34	0.25	42	2.6%	0.29 [−0.08, 0.66]
Cysique-FU 2018: BG	1.4	0.52	73	1.47	0.6	35	2.4%	−0.13 [−0.53, 0.28]
Ernst 2000: BG	9.52	2.14	14	7.63	1.13	12	1.0%	1.05 [0.21, 1.88]
Ernst 2010: BG	3.71	1.28	45	3.3	0.75	46	2.4%	0.39 [−0.03, 0.80]
Kallianpur 2013: BG	0.55	0.61	35	0.35	0.23	12	1.4%	0.36 [−0.30, 1.02]
Koltowska 2010: BG	0.53	0.1	25	0.52	0.11	14	1.4%	0.09 [−0.56, 0.75]
Lee 2003: BG	0.59	0.14	38	0.46	0.07	18	1.6%	1.05 [0.45, 1.64]
Pulliam 2011: BG	2.82	0.61	30	2.73	0.81	7	1.0%	0.14 [−0.69, 0.96]
Sailasuta 2012: BG	0.56	0.09	26	0.59	0.09	10	1.2%	−0.33 [−1.06, 0.41]
Taylor 2007: BG	4.77	1.47	106	4.57	1.17	99	3.1%	0.15 [−0.12, 0.42]
Valcour 2015: BG	5.36	1.18	42	5.72	0.95	27	2.0%	−0.32 [−0.81, 0.16]
VonGiesen 2001: BG	0.53	0.09	32	0.52	0.14	14	1.5%	0.09 [−0.54, 0.72]
Winston 2009: BG	3.34	0.34	10	3.43	0.34	10	0.9%	−0.25 [−1.13, 0.63]
Total (95% CI)			**2374**			**1529**	**100.0%**	**0.14 [0.04, 0.24]**

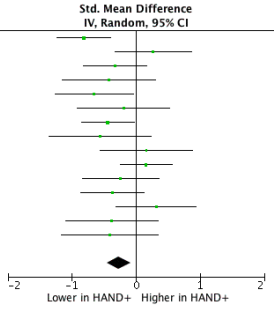
Heterogeneity: Tau² = 0.06; Chi² = 106.13, df = 55 (P < 0.0001); I² = 48%
Test for overall effect: Z = 2.85 (P = 0.004)

B

NAA

Study or Subgroup	HAND+ Mean	SD	Total	HAND− Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2004: FWM	1.67	0.2	61	1.82	0.15	39	9.8%	−0.82 [−1.23, −0.40]
Ernst 2010: FWM	7.99	0.68	18	7.75	0.99	27	6.4%	0.27 [−0.33, 0.87]
Mohamed 2010: FWM	7.34	1.01	65	7.67	0.93	21	8.2%	−0.33 [−0.82, 0.16]
Sailasuta 2016: FWM	11.27	1.15	9	11.82	1.31	41	4.9%	−0.42 [−1.15, 0.31]
Ernst 2010: FGM	7.35	0.85	18	7.93	0.88	27	6.2%	−0.66 [−1.27, −0.04]
Sailasuta 2016: FGM	9.25	1.01	9	9.42	0.83	41	4.9%	−0.19 [−0.92, 0.53]
Chang 2004: PGM	1.51	0.12	61	1.56	0.1	39	10.0%	−0.44 [−0.85, −0.03]
Ernst 2010: PGM	7.71	1.68	10	8.47	1.07	17	4.3%	−0.56 [−1.35, 0.24]
Sailasuta 2016: PGM	14.86	1.44	9	14.65	1.24	41	4.9%	0.16 [−0.56, 0.88]
Chang 2004: BG	1.42	0.21	61	1.39	0.16	39	10.1%	0.15 [−0.25, 0.56]
Ernst 2010: BG	7.34	0.85	18	7.55	0.83	27	6.4%	−0.25 [−0.84, 0.35]
Mohamed 2010: BG	7.13	1.35	65	7.6	1	21	8.1%	−0.37 [−0.86, 0.13]
Roc 2007: BG	1.22	0.1	30	1.19	0.08	15	6.1%	0.31 [−0.31, 0.94]
Sailasuta 2016: BG	9.04	1.48	9	9.63	1.54	41	4.9%	−0.38 [−1.11, 0.35]
VonGiesen 2001: BG	1.49	0.16	22	1.55	0.09	10	4.6%	−0.41 [−1.17, 0.35]
Total (95% CI)			**465**			**446**	**100.0%**	**−0.27 [−0.46, −0.08]**

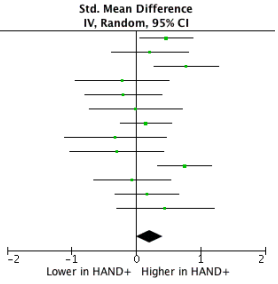
Heterogeneity: Tau² = 0.05; Chi² = 22.01, df = 14 (P = 0.08); I² = 36%
Test for overall effect: Z = 2.82 (P = 0.005)



mI

Study or Subgroup	HAND+ Mean	SD	Total	HAND− Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chang 2004: FWM	0.71	0.13	61	0.66	0.05	39	10.9%	0.47 [0.06, 0.87]
Ernst 2010: FWM	4.39	1.15	18	4.18	0.83	27	7.3%	0.21 [−0.39, 0.81]
Mohamed 2010: FWM	4.01	0.81	65	3.4	0.67	21	8.8%	0.78 [0.27, 1.28]
Sailasuta 2016: FWM	7.98	0.89	9	8.24	1.21	41	5.7%	−0.22 [−0.94, 0.50]
Ernst 2010: FGM	4.94	1.19	18	5.15	0.88	27	7.3%	−0.20 [−0.80, 0.39]
Sailasuta 2016: FGM	6.84	0.64	9	6.85	0.89	41	5.7%	−0.01 [−0.73, 0.71]
Chang 2004: PGM	0.63	0.07	61	0.62	0.06	39	11.0%	0.15 [−0.25, 0.55]
Ernst 2010: PGM	5.24	1.04	10	5.66	1.36	17	5.1%	−0.32 [−1.11, 0.46]
Sailasuta 2016: PGM	7.22	1.17	9	7.56	1.09	41	5.7%	−0.30 [−1.03, 0.42]
Chang 2004: BG	0.61	0.13	61	0.52	0.1	39	10.7%	0.75 [0.33, 1.16]
Ernst 2010: BG	3.66	1.1	18	3.74	1.4	27	7.3%	−0.06 [−0.66, 0.54]
Mohamed 2010: BG	3.21	0.75	65	3.08	0.87	21	9.1%	0.17 [−0.33, 0.66]
VonGiesen 2001: BG	0.54	0.09	22	0.5	0.08	10	5.4%	0.45 [−0.31, 1.20]
Total (95% CI)			**426**			**390**	**100.0%**	**0.20 [−0.00, 0.41]**

Heterogeneity: Tau² = 0.06; Chi² = 21.07, df = 12 (P = 0.05); I² = 43%
Test for overall effect: Z = 1.93 (P = 0.05)



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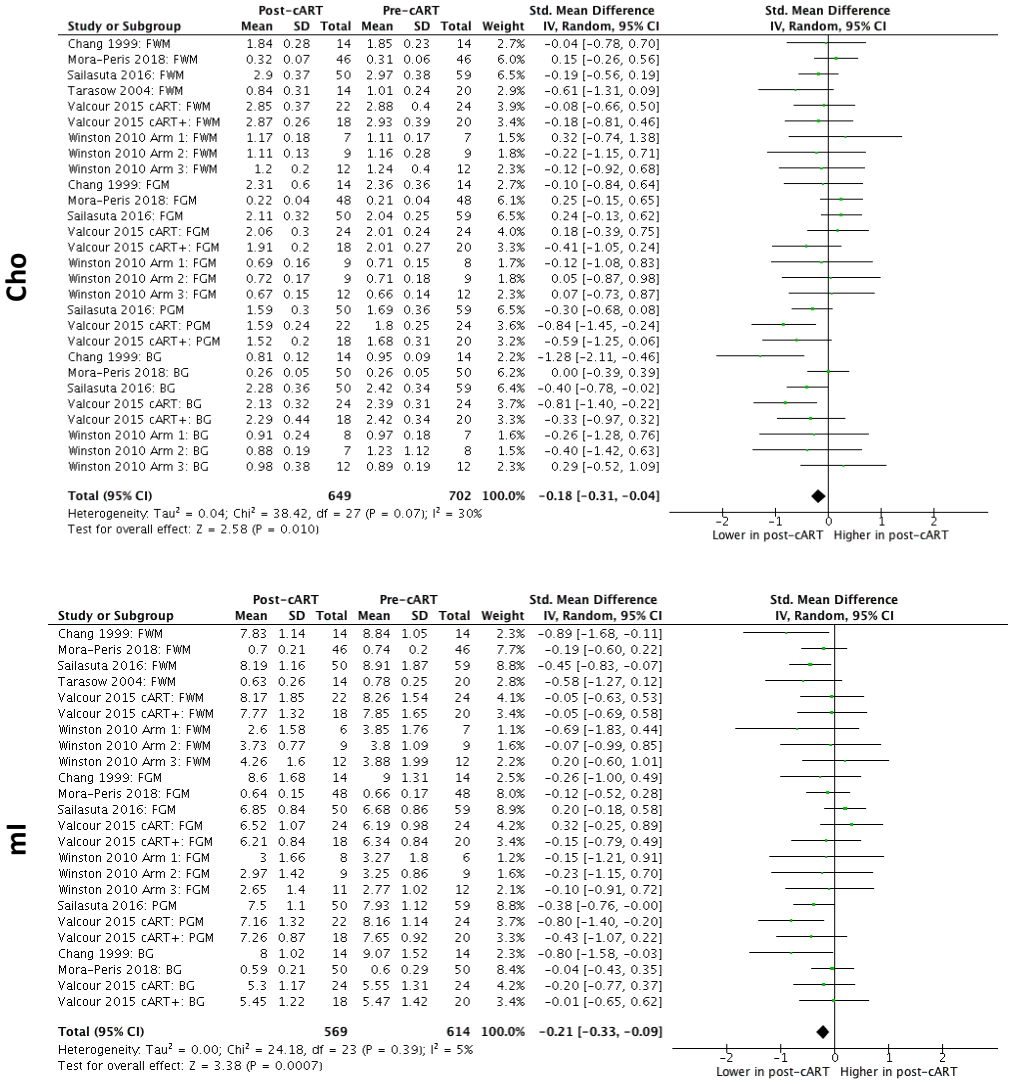


Figure e-5. Study effect sizes of brain metabolites from the secondary meta-analysis that reached significance.

In the secondary meta-analysis, for each metabolite, the data from each region within a single study was treated as an independent study.[1,2] The purpose of this secondary analysis was to estimate "*global*" metabolite alterations. We conducted the secondary meta-analysis for each of the four comparisons (Figures e-1 to e-4), and found significant alterations in metabolites in three comparisons: (**A**) Chronic PWH versus controls; (**B**) Cognitively impaired versus cognitively normal PWH; (**C**) After cART versus before cART in cART-naïve PWH. There was no significant difference for the comparison of acute/early infection PWH versus controls. The complete results are listed in Table 2. Brain regions: BG, the basal ganglia; FWM, the frontal white matter; PWM, the parietal white matter; FGM, the frontal gray matter; PGM, the parietal gray matter. Metabolites: NAA, N-acetyl aspartate; Cho, choline; mI, myo-Inositol; Glx, glutamate (Glu), or a combination of Glu and glutamine (Gln). Cognitive status: CI, cognitively impaired; CN, cognitively normal.

A

NAA

Study or Subgroup	HIV+ Mean	HIV+ SD	HIV+ Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bairwa 2016	8.98	3.2	20	8.3	2.42	30	3.8%	0.24 [-0.33, 0.81]
Bladowska 2013	1.68	0.24	41	1.78	0.24	18	3.9%	-0.41 [-0.97, 0.15]
Boban 2017	1.82	0.42	31	2.08	0.45	41	5.1%	-0.59 [-1.06, -0.11]
Chang 2004	1.56	0.22	100	1.6	0.22	37	7.3%	-0.18 [-0.56, 0.20]
Cysique-BL 2018	4.63	0.6	84	4.75	0.55	42	7.5%	-0.20 [-0.58, 0.17]
Cysique-FU 2018	4.49	0.77	73	4.68	0.74	35	6.6%	-0.25 [-0.65, 0.16]
Ernst 2000	8.82	0.83	24	8.89	0.87	37	4.5%	-0.08 [-0.59, 0.43]
Ernst 2010	7.76	0.99	45	7.76	0.89	46	6.4%	0.00 [-0.41, 0.41]
Kallianpur 2013	1.34	0.12	35	1.3	0.11	12	2.9%	0.33 [-0.33, 0.99]
Koltowska 2010	1.65	0.24	25	1.71	0.21	14	2.9%	-0.26 [-0.91, 0.40]
Lee 2003	1.55	0.21	38	1.59	0.21	18	3.8%	-0.19 [-0.75, 0.37]
Lentz 2009	9.1	1.08	18	10.33	0.51	9	1.7%	-1.27 [-2.15, -0.39]
Pulliam 2011	6.24	1.24	35	6.24	1.11	8	2.2%	0.00 [-0.77, 0.77]
Roc 2007	1.21	0.09	45	1.33	0.19	10	2.5%	-1.04 [-1.76, -0.33]
Sailasuta 2012	1.21	0.25	26	1.26	0.22	10	2.4%	-0.20 [-0.93, 0.53]
Salvan 1997	2.13	0.26	23	2.4	0.59	16	2.9%	-0.62 [-1.28, 0.03]
Tarasow 2004	1.8	0.35	14	1.86	0.3	32	3.2%	-0.19 [-0.82, 0.44]
Taylor 2007	7.37	1	106	7.59	0.94	99	11.1%	-0.23 [-0.50, 0.05]
Valcour 2015	11.37	2.53	42	11.44	2.55	28	5.0%	-0.03 [-0.51, 0.45]
VonGiesen 2001	1.51	0.14	32	1.48	0.17	14	3.2%	0.20 [-0.43, 0.83]
Wilkinson 1997	2.23	0.41	84	2.4	0.43	77	9.5%	-0.40 [-0.72, -0.09]
Winston 2009	1.65	0.25	10	1.72	0.4	10	1.7%	-0.20 [-1.08, 0.68]
Total (95% CI)			**951**			**643**	**100.0%**	**-0.23 [-0.35, -0.11]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 25.46$, df = 21 (P = 0.23); $I^2 = 18\%$
Test for overall effect: Z = 3.77 (P = 0.0002)

Std. Mean Difference
IV, Random, 95% CI

-2 -1 0 1 2
Lower in HIV+ Higher in HIV+

mI

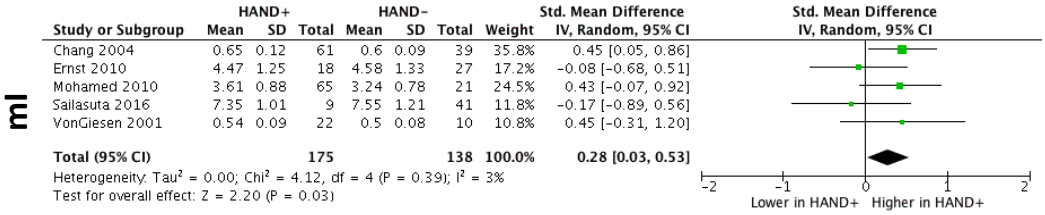
Study or Subgroup	HIV+ Mean	HIV+ SD	HIV+ Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bladowska 2013	0.64	0.14	41	0.65	0.15	18	4.4%	-0.07 [-0.62, 0.49]
Boban 2017	0.56	0.21	31	0.5	0.16	41	6.1%	0.32 [-0.15, 0.79]
Chang 2004	0.63	0.12	100	0.56	0.1	37	9.1%	0.61 [0.22, 0.99]
Cysique-BL 2018	1.12	0.44	84	1.04	0.36	42	9.7%	0.19 [-0.18, 0.56]
Cysique-FU 2018	1.09	0.44	73	1.11	0.48	35	8.3%	-0.04 [-0.45, 0.36]
Ernst 2000	6.05	4.03	24	5.56	2.99	37	5.1%	0.14 [-0.37, 0.66]
Ernst 2010	4.54	1.3	45	4.32	1.19	46	7.9%	0.18 [-0.24, 0.59]
Kallianpur 2013	0.6	0.38	35	0.53	0.2	12	3.1%	0.20 [-0.46, 0.86]
Koltowska 2010	0.63	0.12	25	0.63	0.11	14	3.1%	0.00 [-0.65, 0.65]
Lee 2003	0.63	0.13	38	0.55	0.09	18	4.1%	0.66 [0.09, 1.24]
Lentz 2009	5.23	1.39	18	5.41	1.16	9	2.1%	-0.13 [-0.93, 0.67]
Pulliam 2011	4.48	1.33	35	4.22	1.23	8	2.3%	0.19 [-0.57, 0.96]
Sailasuta 2012	0.67	0.14	26	0.67	0.12	10	2.5%	0.00 [-0.73, 0.73]
Tarasow 2004	0.63	0.26	14	0.62	0.18	32	3.4%	0.05 [-0.58, 0.68]
Taylor 2007	4.37	1.24	106	4.38	1.29	99	17.9%	-0.01 [-0.28, 0.27]
Valcour 2015	6.71	1.57	42	7.19	1.44	28	5.8%	-0.31 [-0.79, 0.17]
VonGiesen 2001	0.53	0.09	32	0.52	0.14	14	3.4%	0.09 [-0.54, 0.72]
Winston 2009	3.71	0.82	10	3.78	0.83	10	1.7%	-0.08 [-0.96, 0.80]
Total (95% CI)			**779**			**510**	**100.0%**	**0.13 [0.01, 0.24]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 16.48$, df = 17 (P = 0.49); $I^2 = 0\%$
Test for overall effect: Z = 2.14 (P = 0.03)

Std. Mean Difference
IV, Random, 95% CI

-2 -1 0 1 2
Lower in HIV+ Higher in HIV+

B



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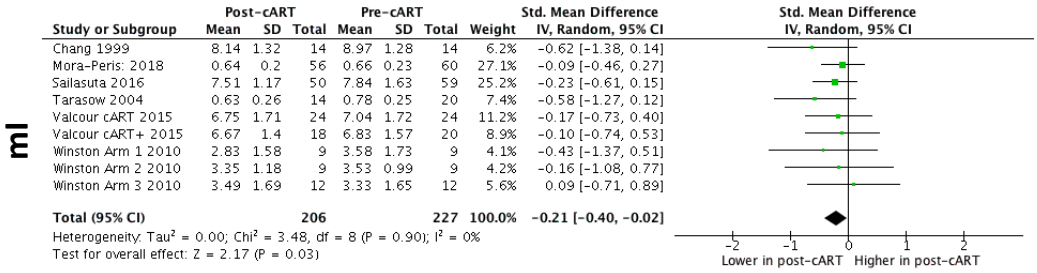

Figure e-6. Study effect sizes of brain metabolites from the tertiary meta-analysis that reached significance (Table e-7).

In the tertiary meta-analysis, the data of each metabolite was first averaged across regions within each study. As metabolites may differ between brain regions, we calculated the average using the same weights for each brain region. The calculated means were then entered into the tertiary meta-analysis.[2,3] Together with the secondary meta-analysis, the tertiary meta-analysis was conducted to examine “global” metabolite alterations. We conducted the tertiary meta-analysis for each of the four comparisons (Figures e-1 to e-4), and found significant alterations in metabolites in three comparisons: (**A**) Chronic PWH versus controls; (**B**) Cognitively impaired versus cognitively normal PWH; (**C**) After cART versus before cART in cART-naïve PWH. Again, there was no significant difference for the comparison of acute/early infection PWH versus controls. The complete results are listed in Table e-7. Metabolites: NAA, N-acetyl aspartate; Cho, choline; mI, myo-Inositol; Glx, glutamate (Glu), or a combination of Glu and glutamine (Gln).

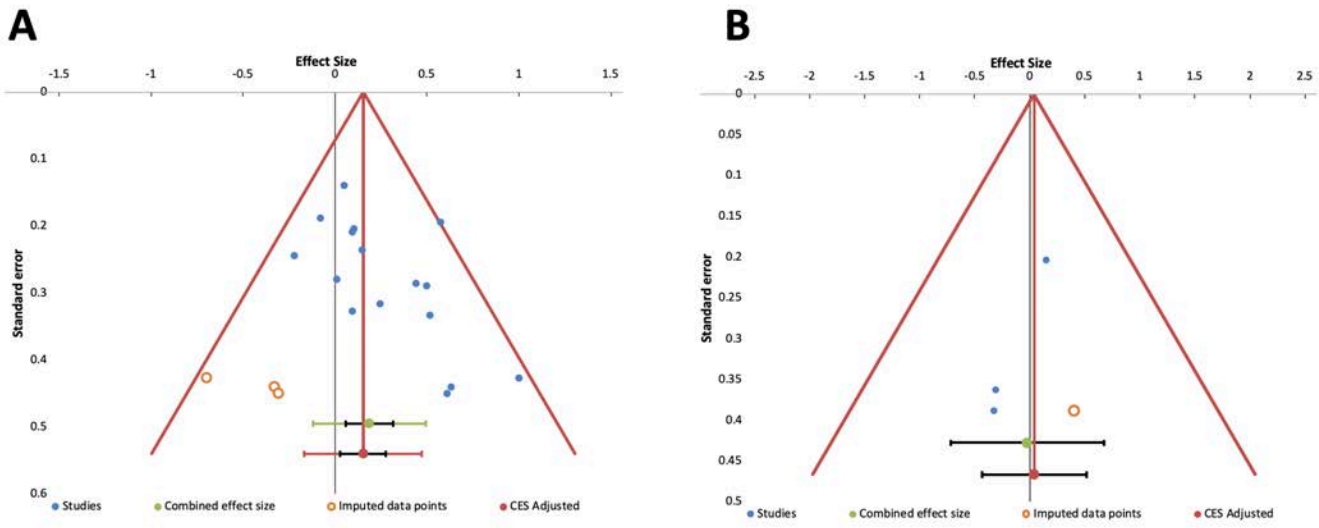

Figure e-7. Funnel plots

Using the Eggers test,[4] publication bias was identified in two metabolites in two comparisons (one in each comparison): choline (Cho) in the frontal white matter (FWM) in the comparison of chronic PWH versus controls (p=0.031); myo-Inositol (mI) in the parietal gray matter (PGM) in the comparison of cognitively impaired versus cognitively normal PWH (p=0.041). The funnel plots of the two comparisons are presented here. (**A**) FWM Cho in the comparison of chronic PWH versus controls; (**B**) PGM mI in the comparison of cognitively impaired versus cognitively normal PWH.

Table e-1. The MRS protocol of all studies included in the quantitative meta-analyses

The quantitative meta-analyses consisted of four comparisons: i) twenty-one studies for chronic PWH versus controls;[5–25] ii) six studies for cognitively impaired PWH versus cognitively normal PWH;[8,11,17,23,26,27] iii) four studies for acute/early HIV infection patients versus controls;[15,18,22,28] and iv) six studies for the impact of antiretroviral treatment in cART-naïve patients.[20,22,27,29–31]

Brain regions: BG, the basal ganglia; FWM, the frontal white matter; PWM, the parietal white matter; FGM, the frontal gray matter; PGM, the parietal gray matter. Metabolites: NAA, N-acetyl aspartate; Cho, choline; mI, myo-Inositol; Glx, glutamate (Glu), or a combination of Glu and glutamine (Gln). Cognitive status: CI, cognitively impaired; CN, cognitively normal. ms, millisecond.

	Study and Year	Cases	Controls	Brain Region	Metabolites	Field Strength	Acquisition Sequence	Voxel Size (cm^3)	Echo Time (ms)
Chronic PWH vs Controls	Bairwa 2016	20	30	FWM, BG	NAA, Cho, Glx, Cr	3	PRESS	4.096 (FWM), 1.728-2.744 (BG)	35
	Bladowska 2013	41	18	FWM, FGM, PWM, PGM, BG	NAA, Cho, mI	1.5	PRESS	8	35
	Boban 2017	31	41	FWM, FGM, PWM, PGM	NAA, Cho, mI	3	PRESS	1	30, 135
	Chang 2004	100	37	FWM, PGM, BG	NAA, Cho, mI	1.5	PRESS	6	35
	Cysique 2018 BL	84	42	FWM, PGM, BG	NAA, Cho, mI, Glx, Cr	3	PRESS	2 (FWM, PGM), 1.5 (BG)	31
	Cysique 2018 FU	73	35	FWM, PGM, BG	NAA, Cho, mI, Glx, Cr	3	PRESS	2 (FWM, PGM), 1.5 (BG)	31
	Ernst 2000	24	37	FGM, PWM, PGM, BG	NAA, Cho, mI, Cr	1.5	STEAM	3--8	30
	Ernst 2010	45	46	FWM, FGM, PGM, BG	NAA, Cho, mI, Glu, Cr	3	PRESS	8	35 to 190
	Kallianpur 2013	35	12	FWM, PGM, BG	NAA, Cho, mI, Glu	3	PRESS	NA	35 to 196
	Koltowska 2010	25	14	FWM, FGM, PWM, PGM, BG	NAA, Cho, mI	1.5	PRESS	8	35
	Lee 2003	38	18	FWM, PGM, BG	NAA, Cho, mI	1.5	PRESS	6	35
	Lentz 2009	10	9	FWM, FGM	NAA, Cho, mI, Glx, Cr	1.5	PRESS	6	35
	Pulliam 2011	35	8	FWM, FGM, BG	NAA, Cho, mI, Glu	4	STEAM	7.5 (FWM), 8 (FGM), 9 (BG)	12
	Roc 2007	45	10	BG	NAA, Cho	30	PRESS	3.125	30, 135
	Sailasuta 2012	26	10	PGM, BG	NAA, Cho, mI, Glx	1.5	PRESS	8 (PGM), 12 (BG)	35
	Salvan 1997	23	16	PWM	NAA, Cho	1.5	PRESS	8	135

	Tarasow 2004	14	32	FWM	NAA, Cho, mI, Cr	1.5	PRESS	8	35
	Taylor 2007	106	99	FWM, FGM, BG	NAA, Cho, mI, Cr	1.5	PRESS	8 (FWM, FGM), 3.375 (BG)	35
	Valcour 2015	42	28	FWM, FGM, PGM, BG	NAA, Cho, mI, Glx, Cr	1.5	PRESS	8 (FWM, FGM, PGM), 12 (BG)	35
	VonGiesen 2001	32	14	BG	NAA, Cho, mI, Glx	1.5	STEAM	8	20
	Wilkinson 1997	84	77	PWM	NAA, Cho	1.5	PRESS	8	20, 135
	Winston 2010	10	10	FWM, FGM, BG	NAA, Cho, mI	1.5	PRESS	NA	36
CI PWH vs CN PWH	Chang 2004	61	39	FWM, PGM, BG	NAA, Cho, mI	1.5	PRESS	6	35
	Ernst 2010	18	27	FWM, PGM, BG	NAA, Cho, mI, Glu, Cr	3	PRESS	8	35 to 190
	Mohamed 2010	65	21	FWM, BG	NAA, Cho, mI, Glx, Cr	3	PRESS	10.648	45
	Roc 2007	30	15	BG	NAA, Cho	30	PRESS	3.125	30, 135
	Sailasuta 2016	9	41	FWM, FGM, PGM, BG	NAA, Cho, mI, Glu, Cr	1.5	PRESS	NA	35
	VonGiesen 2001	22	10	BG	NAA, Cho, mI, Glx	1.5	STEAM	8	20
Acute/Early Infection PWH vs Controls	Chang 2002	45	25	FWM, FGM, BG	NAA, Cho, mI, Cr	1.5	PRESS	NA	30
	Lentz 2009	8	9	FWM, FGM	NAA, Cho, mI, Glx	1.5	PRESS	6	35
	Sailasuta 2012	31	10	PGM, BG	NAA, Cho, mI, Glx	1.5	PRESS	8 (PGM), 12 (BG)	35
	Valcour 2015	62	29	FWM, FGM, PGM, BG	NAA, Cho, mI, Glx, Cr	1.5	PRESS	8 (FWM, FGM, PGM), 12 (BG)	35
After vs Before cART	Chang 1999	14	14	FWM, FGM, BG	NAA, Cho, mI, Cr	1.5	PRESS	3--5	30
	Mora-Peris 2018	60	56	FWM, FGM, BG	NAA, Cho, mI	1.5	PRESS	5.5	36
	Sailasuta 2016	59	50	FWM, FGM, PGM, BG	NAA, Cho, mI, Glu, Cr	1.5	PRESS	NA	35
	Tarasow 2004	20	14	FWM	NAA, Cho, mI, Cr	1.5	PRESS	8	35
	Valcour 2015 cART	24	24	FWM, FGM, PGM, BG	NAA, Cho, mI, Glx, Cr	1.5	PRESS	8 (FWM, FGM, PGM), 12 (BG)	35
	Valcour 2015 cART+	20	18	FWM, FGM, PGM, BG	NAA, Cho, mI, Glx, Cr	1.5	PRESS	8 (FWM, FGM, PGM), 12 (BG)	35
	Winston 2010 Arm 1	9	9	FWM, FGM, BG	NAA, Cho, mI	1.5	PRESS	NA	36
	Winston 2010 Arm 2	9	9	FWM, FGM, BG	NAA, Cho, mI	1.5	PRESS	NA	36

	Winston 2010 Arm 3	12	12	FWM, FGM, BG	NAA, Cho, ml	1.5	PRESS	NA	36

[a] Studies reported both absolute concentration (CSF-correction) or ratio relative to Cr concentration (Cr-scaling). For these studies, the absolute concentration was used in the data analysis.

Table e-2. List of studies included in the chronic PWH versus controls meta-analysis

The demographic and clinical characteristics of chronic PWH (n= 943) include: mean age = 43.1 years, 87.7% male, mean disease duration = 13.2 years, 82.0% on cART, 65.8% with suppressed viral load, CD4 = 439.7 count/μL, and nadir CD4 = 288.3 count/μL. The demographic and clinical characteristics of healthy controls (n= 643) include: mean age = 39.5 years and 81.2% male. NA, data is not available.

Study and Year	Total		Chronic PWH								Controls		
	n	Age (years)	n	Age (years)	% Male	Mean Disease Duration (years)	% taking cART	% suppressed VL	Most Recent CD4 count/μL	Nadir CD4 count/μL	n	Age (years)	% Male
Bairwa 2016	50	35.4	20	37.0	55.0	NA	100.0	NA	257.4	NA	30	34.3	63.3
Bladowska 2013	59	35.7	41	36.1	70.7	NA	48.8[b]	48.8	547.8	307.9	18	34.7	66.7
Boban 2017	72	39.8	31	41.4	90.3	6.4	100.0	100.0	620.3	199.3	41	38.6	90.2
Chang 2004	137	40.0	100	41.3	88.0	NA	93.0	27.0	332.5	NA	37	34.0	49.0
Cysique 2018 BL	126	54.3	84	54.7	100.0	19.0	100.0	97.6	533.4	349.4	42	53.6	100.0
Cysique 2018 FU	108	54.7	73	55.1	100.0	18.6	100.0	97.0	560.0	374.0	35	54.0	100.0
Ernst 2000	61	38.8	24	39.5	87.5	NA	NA	NA	NA	NA	37	38.3	91.9
Ernst 2010	91	44.7	45	46.1	91.1	11.8	NA	NA	409.1	< 500	46	43.3	80.4
Kallianpur 2013	47	53.8	35	53.9	91.4	15.4	100.0	97.1	529.6	163.4	12	53.5	100.0
Koltowska 2010	39	35.1	25	35.4	40.0	NA	NA	NA	NA	NA	14	34.5	64.3
Lee 2003	56	NA	38	NA	NA	NA	NA	NA	NA	NA	18	NA	NA
Lentz 2009	19	NA	10	NA	NA	>4	100.0	NA	453.0	NA	9	32.0	NA
Pulliam 2011	43	50.2	35	NA	100.0	17.0	100.0	54.3	NA	NA	8	NA	100.0
Roc 2007	55	42.7	45	42.0	71.1	NA	71.1	NA	380.2[a]	< 500	10	46.0	60.0
Sailasuta 2012	36	34.6	26	34.0	50.0	NA	NA	NA	215.0	NA	10	36.0	60.0
Salvan 1997	39	35.0[a]	23	NA	NA	NA	NA	NA	NA	NA	16	NA	NA
Tarasow 2004	46	35.4	14	35.4	85.7	NA	100.0	NA	172.6	NA	32	35.4	87.5
Taylor 2007	205	37.6	106	38.2	87.7	NA	62.3	43.2	429.6	246.3	99	36.9	70.7
Valcour 2015	70	31.2	42	29.0[a]	90.5	0.5	100.0	85.7	445.1[a]	NA	28	34.4[a]	53.6
VonGiesen 2001	46	39.4	32	42.0	100.0	6.9	90.6	50.0	472.0	NA	14	33.6	100.0
Wilkinson 1997	161	37.0	84	38.0	100.0	NA	41.7	NA	390.6	NA	77	36.0	100.0
Winston 2010	20	35.5	10	39.0	NA	5.8	60.0	60.0	392.0	228.0	10	32.0	NA

[a] **Median**

[b] **cART naïve patients with no need for cART according to European AIDS Clinical Society (EACS) recommendations were included**

Table e-3. List of studies included in the cognitively impaired PWH versus cognitively normal PWH meta-analysis

The demographic and clinical characteristics of cognitively impaired (CI) PWH (n= 205) include: mean age = 44.4 years, 80.8% male, mean disease duration = 8.3 years, 94.1% on cART, 40.7% with suppressed viral load, and CD4 = 385.7 count/μL. The demographic and clinical characteristics of cognitively normal (CN) PWH (n= 153) include: mean age = 42.5 years; 84.5% male, mean disease duration = 11.4 years, 90.5% on cART; 18.4% with suppressed viral load, and CD4 = 371 count/μL. NA, data is not available.

Study and Year	CI PLWH							CN PLWH						
	n	Age (years)	% Male	Mean Disease Duration (years)	% taking cART	Most Recent CD4 count/μL	Nadir CD4 count/μL	n	Age (years)	% Male	Mean Disease Duration (years)	% taking cART	Most Recent CD4 count/μL	Nadir CD4 count/μL
Chang 2004	61	44.0	89.0	NA	98.4	343.0	NA	39	37.0	87.0	NA	84.6	316.0	NA
Ernst 2010	18	45.0	89.0	10.4	NA	439.8	< 500	27	46.8	96.0	12.8	NA	388.7	< 500
Mohamed 2010	65	47.2	69.2	NA	100	394.0	NA	21	46.1	66.0	NA	100.0	364.0	NA
Roc 2007	30	41.0	70.0	NA	76.7	383.8[a]	< 500	15	44.0	73.0	NA	60.0	373.0[a]	< 500
Sailasuta 2016	9	NA	NA	NA	100	NA	< 350	41	NA	NA	NA	100.0	NA	< 350
VonGiesen 2001	22	41.5	100.0	6.5	86.4	435	NA	10	43.1	100.0	7.8	100.0	553.0	NA

[a] Median

Table e-4. List of studies included in the PWH with acute/early infection versus controls meta-analysis

The demographic and clinical characteristics of acute PWH (n= 146) include: mean age = 33.9 years, 89.1% male, mean disease duration = 0.76 years, 0% on cART, and CD4 =220.4 count/μL. The demographic and clinical characteristics of healthy controls include: mean age = 33.5 years and 54.6% male. NA, data is not available.

Study and Year	Total		Acute/Early PWH							Controls		
	n	Age (years)	n	Age (years)	% Male	Mean Disease Duration (years)	% taking cART	% suppressed VL	Most Recent CD4 count/μL	n	Age (years)	% Male
Chang 2002	70	34.5	45	35.7	84.4	1.9	0.0	NA	184.4	25	32.2	52.0
Lentz 2009	17	35.3	8	39.0	100.0	0.2	0.0	0.0	423.0	9	32.0	NA
Sailasuta 2012	41	31.5	31	30.0	84.0	0.04[a]	0.0	NA	428.0[a]	10	36.0	60.0
Valcour 2015	91	NA	62	27.5[a]	93.5	0.05	0.0	NA	380.4[a]	29	35.0[a]	55.0

[a] Median

Table e-5. List of studies included in the after versus before cART meta-analysis

The demographic and clinical characteristics of pre-cART PWH with acute infection (n= 227) include: mean age = 35.0 years, 78.7% male; 0% on cART, 5.2% with suppressed viral load, CD4 = 283 count/μL, and nadir CD4 = 185.1 count/μL. The demographic and clinical characteristics of post-cART PWH (n= 206) with acute infection include: mean age = 37.4 years, 91.4% male, 100% on cART, 84.9% with suppressed viral load, CD4 = 438.5 count/μL, and nadir CD4 = 185.1 count/μL. NA, data is not available.

Study and Year	Time Delay (weeks)	Pre-cART							Post-cART						
		n	Age	% Male	Mean Disease Duration (years)	% taking cART	Most Recent CD4 count/μL	Nadir CD4 count/μL	n	Age	% Male	Mean Disease Duration (years)	% taking cART	Most Recent CD4 count/μL	Nadir CD4 count/μL
Chang 1999	43	14	44.9	100.0	6.0	0.0[b]	165.9	< 200	14	45	100	6.0	100.0	299.3	< 200
Mora-Peris 2018	48	60	33.0	96.7	NA	0.0	441.0	NA	56	NA	NA	NA	100.0	615.0	NA
Sailasuta 2016	52	59	35.0	42.4	NA	0.0	233.0	< 350	50	NA	NA	NA	100.0	412.0	< 350
Tarasow 2004	26	20	34.6	90.0	NA	0.0	137.8	NA	14	35.4	85.7	NA	100	173	NA
Valcour 2015 cART[c]	24	24	28.5[a]	91.7	< 0.1	0.0	439.4[a]	NA	24	28.5[a]	91.7	< 0.1	100	660.7[a]	NA
Valcour 2015 cART+[c]	24	20	32.3[a]	90.0	< 0.1	0.0	454.2[a]	NA	18	30.4[a]	88.9	< 0.1	100	626.4[a]	NA
Winston 2010 Arm 1[c]	48	9	35.0	NA	NA	0.0	235.0	170.0	9	35.0	NA	NA	100.0	299.0	170.0
Winston 2010 Arm 2[c]	48	9	37.0	NA	NA	0	194.0	171.0	9	37.0	NA	NA	100.0	400.0	171.0
Winston 2010 Arm 3[c]	48	12	33.0	NA	NA	0	222.0	207.0	12	33.0	NA	NA	100.0	331.0	207.0

[a] Median

[b] 78.6% of subjects were taking 1-2 antiretroviral medications at baseline. No subjects had been treated with cART prior to start of study.

[c] PWH were randomized into different groups to receive different antiretroviral treatment plans, including two groups in Valcour et al. (2015), and three groups in Winston et al. (2010).

Table e-6. List of studies included in the additional qualitative analysis for the associations between cognitive impairment/performance and metabolite alterations

In addition to the quantitative analysis, we conducted an additional qualitative data analysis to further evaluate the associations between metabolite alterations and cognitive impairment in PWH. In this qualitative analysis, we first identified all HIV MRS studies that investigated the impact of cognitive impairment/performance on brain metabolites and excluded publications that were based on the same subject cohort. In the end, 17 studies were selected for the qualitative analysis, which included 11 additional studies that were not included in the quantitative meta-analysis due to a lack of available data (i.e., only bar graphs or regression analysis without mean and SD) [8,9,11,16,26,28,32–42]. Then for each metabolite, we summarized the number of studies (out of 17) that examined this metabolite (at any region) and the number of studies that identified a significant effect of cognitive impairment on the metabolite signal (at one or more brain regions). This qualitative analysis was more inclusive than the quantitative meta-analysis (17 versus 6 studies, and 1585 versus 358 PWH), and provided additional support for an important role of NAA reduction in cognitive impairment in PWH.

The demographic and clinical characteristics of cognitively impaired (CI) PWH (n= 723) include: mean age = 45.3 years, 81.8% male, mean disease duration = 10.5 years, 88.1% on cART, 59.9% with suppressed viral load, and CD4 = 370.7 count/μL. The demographic and clinical characteristics of cognitively normal (CN) PWH (n= 755) include: mean age = 45.0 years, 83.3% male, mean disease duration = 9.6 years, 85.5% on cART, 68.6% with suppressed viral load, and CD4 = 397 count/μL. NA, data is not available.

Study and Year	Total		CI PLWH							CN PLWH						
	n	Age (years)	n	Age (years)	% Male	Mean Disease Duration (years)	% taking cART	Most Recent CD4 count/ uL	Nadir CD4 count/μL	n	Age (years)	% Male	Mean Disease Duration (years)	% taking cART	Most Recent CD4 count/ uL	Nadir CD4 count/μL
Alakkas 2019	253	44.1	101	NA	NA	NA	NA	NA	NA	152	NA	NA	NA	NA	NA	NA
Campbell 2020	241	45.0	97	43.6	76.3	13.1[a]	83.5	481.0[a]	150.0[a]	144	46.0	83.3	11.0[a]	74.3	442.0[a]	150.6[a]
Chang 2002	45	35.7	35	NA	NA	NA	0.0	NA	NA	10	NA	NA	NA	0.0	NA	NA
Chang 2004	100	41.3	61	44.0	89.0	NA	98.0	343.0	NA	39	37.0	87.0	NA	82.0	316.0	NA
Chang 2005	68	37.3	NA	NA	NA	NA	NA	< 500	NA	NA	NA	NA	NA	NA	NA	NA
Cysique 2013	92	55.7	21	NA	NA	NA	100.0	NA	< 350	71	NA	NA	NA	100.0	NA	< 350
Cysique 2018	73	45+	41	45+	NA	NA	NA	NA	NA	32	45+	NA	NA	NA	NA	NA
Ernst 2010	45	46.1	18	45.0	89.0	0.3	NA	439.8	< 500	27	46.8	96.0	0.4	NA	388.7	< 500

Study and Year	Total		CI PLWH							CN PLWH						
	n	Age (years)	n	Age (years)	% Male	Mean Disease Duration (years)	% taking cART	Most Recent CD4 count/ uL	Nadir CD4 count/µL	n	Age (years)	% Male	Mean Disease Duration (years)	% taking cART	Most Recent CD4 count/ uL	Nadir CD4 count/µL
Harezlak 2011	240	47.0	116	47.9[a]	87.1	12.1[a]	92.2	303.7[a]	37.4[a]	124	44.5[a]	83.0	12.0[a]	90.0	312.0[a]	31.0[a]
Ignjatovic 2018	39	42.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mohamed_Pomper 2010	74	41.1	34	41.2	59.0	NA	100.0	151.0	NA	40	41.0	75.0	NA	100.0	169.0	NA
Mohamed_Sacktor 2010	86	46.9	65	47.2	69.2	NA	100.0	394.0	NA	21	46.1	66.0	NA	100.0	364.0	NA
Mohamed 2018	45	58.9	21	58.2	76.0	19.2	100.0	676.0	NA	24	59.6	71.0	19.9	100.0	674.0	NA
Patel 2003	15	39.1	7	45.0	85.7	NA	NA	NA	NA	8	34.0	75.0	NA	NA	NA	NA
Paul 2007	114	41.9	75	43.4[a]	90.7	NA	96.0	302.3[a]	NA	39	37.0[a]	89.0	NA	78.0	284.0[a]	NA
Pulliam 2011	35	50.2	16	NA	100.0	NA	NA	NA	NA	19	NA	100.0	NA	NA	NA	NA
Sacktor 2005	20	42.9	15	44.1[a]	87.1	NA	100.0	151.1[a]	NA	5	39.0[a]	100.0	NA	100.0	178.0[a]	NA

[a] **Median**

Table e-7. The tertiary meta-analysis results summary

CI, cognitively impaired; CN, cognitively normal.

	Metabolites	Studies	Cases	Controls	Effect Size			Heterogeneity	
					95% CI	P	P-FDR	I^2, %	P
Chronic PWH vs Controls	NAA	22	951	643	-0.23 (-0.35 to -0.11)	**0.0002**	**0.001**	18.00	0.230
	Cho	22	951	643	0.10 (-0.01 to 0.20)	0.070	0.093	0.00	0.960
	mI	18	779	510	0.13 (0.01 to 0.24)	**0.030**	0.060	0.00	0.490
	Glx	10	410	234	0.03 (-0.14 to 0.19)	0.760	0.760	0.00	0.880
CI PWH vs CN PWH	NAA	6	205	153	-0.21 (-0.44 to 0.02)	0.070	0.140	0.00	0.620
	Cho	6	205	153	-0.26 (-0.80 to 0.29)	0.360	0.480	80.00	0.0001
	mI	5	175	138	0.28 (0.03 to 0.53)	**0.030**	0.120	3.00	0.390
	Glx	4	114	99	-0.08 (-0.45 to 0.29)	0.680	0.680	29.00	0.240
Acute/Early Infection PWH vs Controls	NAA	4	128	72	-0.04 (-0.42 to 0.35)	0.850	0.990	35.00	0.200
	Cho	4	128	72	0.25 (-0.28 to 0.79)	0.360	0.990	65.00	0.040
	mI	4	128	72	0.00 (-0.43 to 0.43)	0.990	0.990	48.00	0.120
	Glx	4	128	72	0.07 (-0.22 to 0.37)	0.630	0.990	0.00	0.610
After vs Before cART	NAA	9	227	206	-0.02 (-0.21 to 0.17)	0.810	0.810	0.00	0.990
	Cho	9	227	206	0.09 (-0.10 to 0.28)	0.370	0.740	0.00	0.820
	mI	9	227	206	0.21 (0.02 to 0.40)	**0.030**	0.120	0.00	0.900
	Glx	3	103	92	-0.10 (-0.83 to 0.63)	0.790	0.810	83.00	0.003

Table e-8. The results summary of the two sensitivity analyses

For the first sensitivity analysis, each study was temporarily removed one-at-a-time in order to assess how this change affected the significance of each comparison. For the second sensitivity analysis, all studies from the same research group were temporarily removed altogether in order to assess how this change impacted the significance of each comparison. Both sensitivity analyses showed that all significant results that survived correction for multiple comparison were robust and remained significant. The results that changed from $p<0.05$ to $p>0.05$ (uncorrected) or $p>0.05$ to $p<0.05$ (uncorrected) were listed below.

Analysis	Brain Region	Metabolite	Stud(ies) Removed Which Affected Significance	Original P	New P
Chronic PWH vs Controls[b]	FWM	Glx	Cysique 2018 BL, Cysique 2018 FU	0.02	0.07
Chronic PWH vs Controls[b]	BG	mI	Ernst 2000, Ernst 2010, Chang 2004	0.03	0.28
CI PWH vs CN PWH[a]	FWM	NAA	Ernst 2010	0.14	0.0006
CI PWH vs CN PWH[a]	FWM	mI	Chang 2004	0.04	0.3
CI PWH vs CN PWH[a]	FWM	mI	Ernst 2010	0.04	0.1
CI PWH vs CN PWH[a]	FWM	mI	Mohamed 2010	0.04	0.19
CI PWH vs CN PWH[a]	BG	mI	Ernst 2010	0.07	0.02
After vs Before cART[a]	FGM	NAA	Chang 1999	0.07	0.03
After vs Before cART[a]	FGM	NAA	Mora-Peris 2018	0.07	0.02
After vs Before cART[b]	BG	Cho	Valcour 2015 cART, Valcour 2015 cART+	0.02	0.11

[a]Leave-one-study-out sensitivity analysis

[b]Leave-one-team-out sensitivity analysis

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