(NEURO)INFLAMMATORY BIOMARKERS MEDIATE THE ASSOCIATION BETWEEN HIV AND DEPRESSION

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on behalf of the COmorBidity in Relation to AIDS (COBRA) cohort

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BACKGROUND

- People with HIV are at increased risk for depression, though the underlying mechanisms for this are unclear.
- In the general population, depression is associated with peripheral and central inflammation.
- Since HIV infection may elicit (neuro)inflammation, **we hypothesised that (neuro)inflammatory biomarkers would mediate the association between HIV and depressive symptoms.**

METHODS

- *N* = 204: 125 people with HIV, 79 people without HIV in the COmorBidity in Relation to AIDS (COBRA) study, a prospective cohort of adults living with HIV in London and Amsterdam were included. (PMID: 29596425)
- **Depressive symptoms** were measured using the Patient Health Questionnaire (PHQ-9). A total PHQ-9 score ≥ 4 was considered as "Any Depressive Symptoms".
- **Systemic and central nervous system inflammation** was measured using blood plasma, CSF, and brain MRS imaging biomarkers.

Table 1. Summary of biomarkers included in the study:

Biomarker		Sample Size (*N*)			
		Total	***PHQ9≥4***	***Total***	***PHQ9≥4***
		FWM		*Putamen*	
Magnetic Resonance Spectroscopy	Myo-inositol	161	29	63	20
	Choline	184	36	128	29
		Plasma		*CSF*	
Soluble biomarkers *measured in all participants, where possible*	CRP	204	42	-	-
	I-FABP	202	41	-	-
	Kyn:Trp Index	203	41	202	41
	Neopterin	203	41	202	41
	NFL	202	41	203	41
	sCD14	201	40	202	41
	sCD16	202	42	-	-
	sCD163	204	42	203	41
		Plasma		*CSF*	
Soluble biomarkers *measured in a subset of participants*	IL-6	78	13	78	13
	IP-10	78	13	78	13
	MCP-1	78	13	78	13
	MIG	78	13	78	13
	MIP1α	78	13	78	13
	RANTES	78	13	78	13
	TNF-α	78	13	78	13

CSF: cerebrospinal fluid; FWM: frontal white matter

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STATISTICAL ANALYSIS

We used logistic regression to explore the potential mediating role of biomarkers on the association between HIV status and "Any Depressive Symptoms" (PHQ-9 score ≥ 4). Models were adjusted for sociodemographic factors: age (years, continuous), sex, ethnicity, and years of education (continuous). Models involving any neurometabolite measures were also corrected for MRI scanner. We then sequentially adjusted the model for each biomarker separately. **Individual biomarkers for which adjustment resulted in a >10% reduction in the Odds Ratio (OR) were considered potential mediators of the association between HIV status and Any Depressive Symptoms**.

RESULTS

- Participants were 93% male, 92% White, 83% men who have sex with men, with median (IQR) age 57 (51, 62) years and CD4 615 (472, 798) copies/ml. Median years since HIV diagnosis was 14.8 (9,18) years. All had HIV-RNA viral load of < 200 copies/ mL.
- Of the biomarkers analysed, our criterion for potential mediation was met for plasma MIG (change in OR_{HIV}: -15.0%), plasma TNF-α (-11.4%), CSF MIP1-α (-21.0%), and CSF IL-6 (-18.0%). None of the other neuroimaging, plasma, or CSF biomarkers met our criterion of >10% reduction in OR (Fig.1).

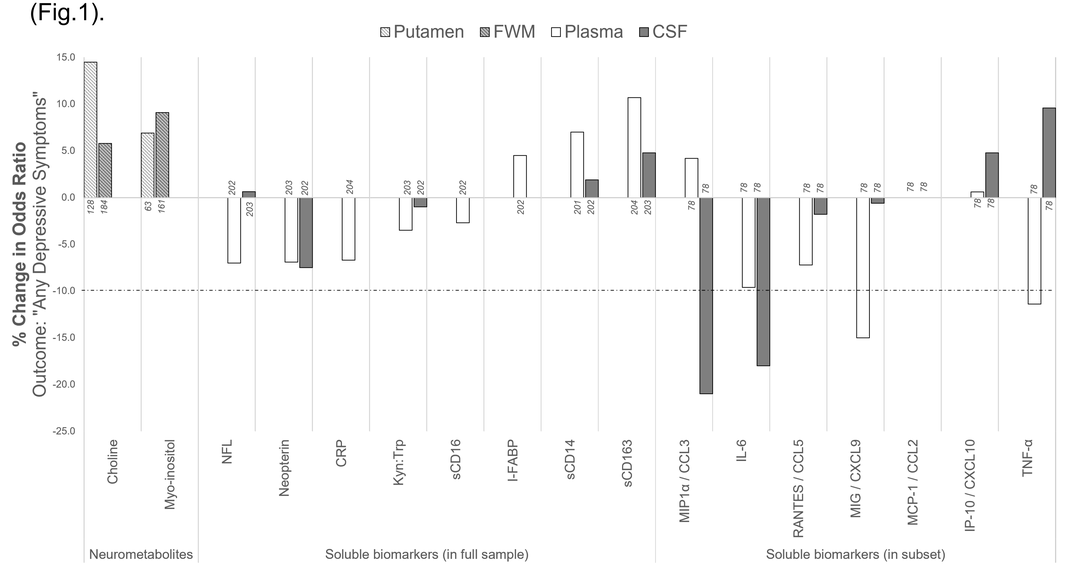


Figure 1. Mediation of the association between HIV status and Any Depressive Symptoms by each biomarker separately. The dotted line marks a 10% reduction in Odds Ratio, which represents our criterion for potential mediation.

In a sample of 125 people living with HIV and 79 people without HIV, the biomarkers MIG and TNF-α in plasma and MIP1-α and IL-6 in CSF mediated the association between HIV status and depressive symptoms.

Table 2. Odds Ratios (OR, with 95% confidence interval [CI]) for the association between HIV status and Depressive Symptoms

Biomarker	OR (95% CI) for Any Depressive Symptoms	
	Before adjusting for biomarker	**Adjusted for biomarker**
Neurometabolites		
Myo-inositol		
Frontal White Matter	2.96 (1.12, 9.13)	3.23 (1.19, 10.15)
Putamen	5.19 (1.32, 27.63)	5.55 (1.35, 30.35)
Choline		
Frontal White Matter	2.75 (1.17, 7.20)	2.91 (1.21, 7.74)
Putamen	7.46 (2.26, 35.53)	8.54 (2.50, 41.47)
Soluble biomarkers *measured in all participants, where possible*		
	Plasma	
CRP	3.27 (1.46, 8.09)	3.05 (1.34, 7.61)
I-FABP	3.81 (1.65, 9.91)	3.98 (1.62, 10.86)
Kyn:Trp	3.76 (1.63, 9.78)	3.63 (1.54, 9.59)
Neopterin	3.76 (1.63, 9.78)	3.50 (1.44, 9.45)
NFL	3.16 (1.41, 7.80)	2.94 (1.29, 7.31)
sCD14	3.01 (1.34, 7.49)	3.22 (1.39, 8.20)
sCD16	3.36 (1.50, 8.30)	3.27 (1.44, 8.18)
sCD163	3.27 (1.46, 8.09)	3.62 (1.59, 9.11)
	CSF	
Kyn:Trp	3.07 (1.37, 7.57)	3.04 (1.34, 7.62)
Neopterin	3.07 (1.37, 7.57)	2.84 (1.25, 7.11)
NFL	3.13 (1.40, 7.80)	3.15 (1.40, 7.82)
sCD14	3.08 (1.38, 7.62)	3.14 (1.39, 7.78)
sCD163	3.13 (1.40, 7.72)	3.28 (1.46, 8.13)
Soluble biomarkers *measured in a subset of 78 participants*		
	Plasma	
IL-6	1.67 (0.46, 6.58)	1.51 (0.40, 6.01)
IP-10 / CXCL10	1.67 (0.46, 6.58)	1.68 (0.45, 6.69)
MCP-1 / CCL2	1.67 (0.46, 6.58)	1.67 (0.46, 6.59)
MIG / CXCL9	1.67 (0.46, 6.58)	1.42 (0.38, 5.63)
MIP1-α / CCL3	1.67 (0.46, 6.58)	1.74 (0.47, 7.00)
RANTES / CCL5	1.67 (0.46, 6.58)	1.55 (0.41, 6.20)
TNF-α	1.67 (0.46, 6.58)	1.48 (0.39, 5.98)
	CSF	
IL-6	1.67 (0.46, 6.58)	1.37 (0.35, 5.59)
IP-10 / CXCL10	1.67 (0.46, 6.58)	1.75 (0.46, 7.16)
MCP-1 / CCL2	1.67 (0.46, 6.58)	1.67 (0.45, 6.58)
MIG / CXCL9	1.67 (0.46, 6.58)	1.66 (0.45, 6.58)
MIP1-α / CCL3	1.67 (0.46, 6.58)	1.32 (0.35, 5.26)
RANTES / CCL5	1.67 (0.46, 6.58)	1.64 (0.45, 6.47)
TNF-α	1.67 (0.46, 6.58)	1.83 (0.49, 7.31)

CONCLUSIONS

- Four biomarkers of inflammation – MIG and TNF-α in plasma, and MIP1-α and IL-6 in CSF – are potential mediators of the association between HIV status and depressive symptoms.
- Some limitations of the study include: analyses restricted to participants without severe depressive symptoms (PHQ-9 > 15); lack of gender and ethnic diversity limits generalisation.

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