Inflammatory Biomarker Profiling to Predict Neuroinflammation and Depression in Adolescents With HIV

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BACKGROUND

- Adolescents with perinatally acquired HIV (PHIV) face a heightened risk of neuroinflammation due to persistent immune activation, even on suppressive antiretroviral therapy (ART).
- Chronic inflammation is strongly linked to depression, which is prevalent in PHIV adolescents and significantly impacts quality of life and ART adherence.
- Blood-based inflammatory biomarkers can provide insight into neuroinflammatory processes and serve as early indicators of mental health risks.

Aim

To identify early inflammatory biomarkers predictive of neuroinflammation and depression in adolescents with perinatally acquired HIV (PHIV) using longitudinal data from the CHER trial.

METHODS

Neuro-psychiatric Measures

Depression Assessments
Measured at 16 years of age; n=39
Tool: Nine-item Patient Health Questionnaire (PHQ-9)

Brain Metabolites
Measured at 11 years of age
Technique: Magnetic Resonance Spectroscopy (MRS)
Measured Metabolites: Choline (associated with cell membrane turnover) and Myo-inositol (associated with glial activation)
Regions of interest: Basal Ganglia (BG), Midfrontal Gray Matter (MFGM), and Petrigonal White Matter (PWM)

Immune Biomarkers

Plasma Immune Markers
Measured at pre-ART, 1, 2, 3-4, 5 years post-ART, and at 8 years
Technique: Luminex Multiplex Assays and ELISAs
Markers: IL-17F, IL-1β, IL-1α, TNFα, TNFβ, GCSF, GMCSF, IL-14, IFN-α, IL-2, IL-5, IL-6, IL-7, IL-3, IL-12, IL-15, IL-17A, IP-10, IFN-γ, MCP-1, MIP-1α, MIP-1β, CD40L, VEGF, FGF, RANTES, PDGFBB, sCD163, IL-18, hsCRP, S100A8/A9, IL-4, IL-10, IL-9, TGFβ, sCD14, LBP, I-FABP, MAdCAM-1

HIV Persistence

Subset Analysis
Measured pre-ART and at 8 years of age
Integrase Cell-Associated HIV-1 DNA (iCAD) as a marker of HIV persistence

RESULTS

Early-life blood biomarkers and severity of depressive symptoms in adolescence

Table 1: Summary of demographic and clinical characteristics for participants, stratified by depressive symptom status

Characteristic	Overall, *N* = 39	Any Depressive Symptoms, *n* = 17	No Depressive Symptoms, *n* = 22	p-value
Age (years), Median (IQR)	16.0 (15.0, 16.0)	16.0 (15.0, 16.0)	16.0 (15.3, 16.0)	0.2
Gender, n (%)				0.4
Boy	17 (44%)	6 (35%)	11 (50%)	
Girl	22 (56%)	11 (65%)	11 (50%)	
Ethnicity, n (%)				0.6
Black/African	34 (87%)	14 (82%)	20 (91%)	
Coloured	5 (13%)	3 (18%)	2 (9.1%)	
Antiretroviral Therapy Regimen, n (%)				0.6
ABC/3TC	1 (2.6%)	1 (5.9%)	0 (0%)	
Atazanavir	4 (10%)	2 (12%)	2 (9.1%)	
DTG	1 (2.6%)	1 (5.9%)	0 (0%)	
Efavirenz	1 (2.6%)	1 (5.9%)	0 (0%)	
F/TAF	1 (2.6%)	0 (0%)	1 (4.5%)	
LPV/r	4 (10%)	1 (5.9%)	3 (14%)	
TLD	27 (69%)	11 (65%)	16 (73%)	
HIV Viral Load < 200 copies/mL, n (%)	35 (90%)	16 (94%)	19 (86%)	0.6
Total PHQ-9 Score, Median (IQR)	4.0 (0.0, 8.0)	9.0 (7.0, 13.0)	0.5 (0.0, 3.0)	**<0.001**

Participants with total PHQ-9 score > 4 were classified as exhibiting "any depressive symptoms" and those with PHQ-9 score ≤ 4 were classed as exhibiting "no depressive symptoms". Bold text indicates statistically significant ($p < 0.05$) difference between groups. **Abbreviations –** ABC/3TC: abacavir + lamivudine; DTG: dolutegravir; F/TAF: emtricitabine + tenofovir alafenamide; IQR: interquartile range; LPV/r: lopinavir + ritonavir; PHQ-9: patient health questionnaire (nine-item); TLD: tenefovir disoproxil fumarate + lamivudine + dolutegravir.

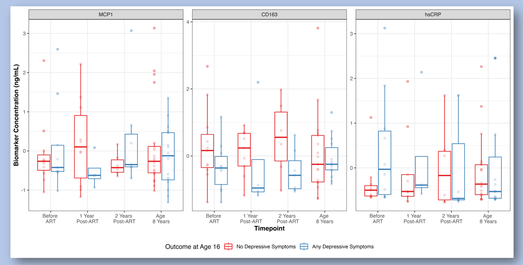


Figure 1: Early-life inflammatory biomarkers and incidence of any depressive symptoms in adolescence. Participants were grouped as exhibiting any depressive symptoms (defined as PHQ-9 > 4, n = 17) or no depressive symptoms (PHQ-9 ≤ 4, n = 22). The middle line in each box plot represents the median, with the upper and lower hinges representing the third and first quartile, respectively

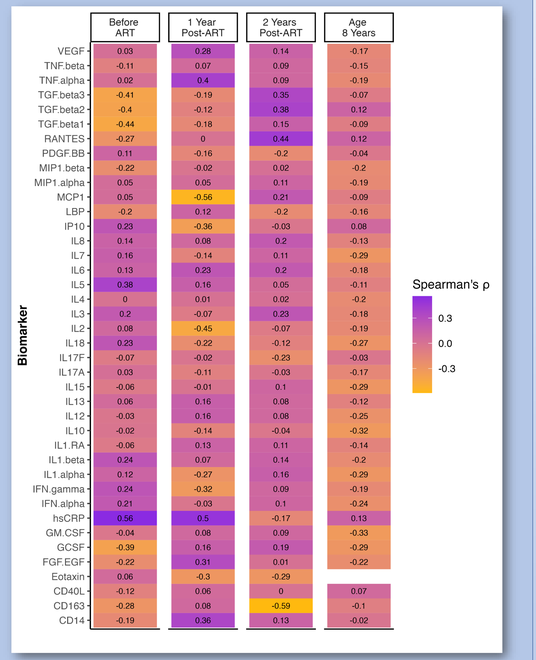


Figure 2: Early-life inflammatory biomarkers and depressive symptom severity in adolescence. Heatmap of Spearman's correlations (ρ) for inflammatory biomarkers in blood plasma and depressive symptom severity at age 16 years. Strength of correlations is represented by a colour gradient from –1.0 (bright yellow) to +1.0 (bright purple), with in-laid text in tiles indicating these magnitudes

Early-life blood biomarkers associations with brain metabolic profiles

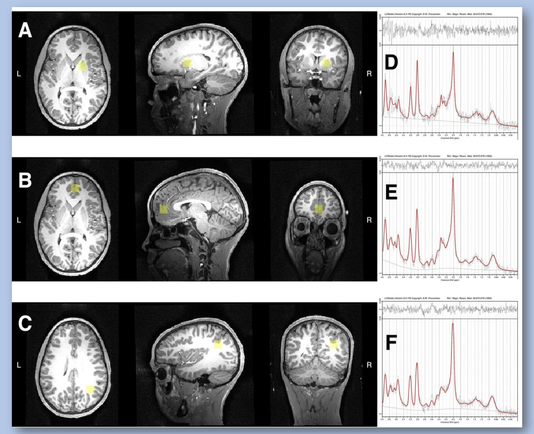


Figure 3: Voxels of interest and representative MRS spectra from one participant. (A-C) Positions of the voxels of interest (VOI, in yellow) in the (A) basal ganglia (BG), (B) midfrontal gray matter (MFGM), and (C) peritrigonal white matter (PWM), and (D-F) corresponding MRS spectra from the VOIs in (D) BG, (E) MFGM, and (F) PWM. Voxel placement images were produced using Gannet software: https://www.fil.ion.ucl.ac.uk/spm/software/spm12/

Table 2: Summary of correlation analysis between brain metabolite (per brain region) and immune biomarker measures

Brain region of interest	Metabolite	Correlated Biomarker	Correlation (r)	p-value
BG	Choline	TNFβ	+0.61	0.02
	Choline/Cr	IL-13	+0.54	0.04
		IL-17F	+0.63	<0.01
		TNFβ	+0.71	<0.01
		LBP	+0.56	0.02
	Myo-inositol/Cr	IL-13	+0.65	<0.01
		TNFβ	+0.81	<0.01
		IL-17F	+0.73	<0.01
MFGM	Choline	CD40L	+0.54	0.02
		IL-17F	+0.55	0.02
		TNFβ	+0.51	0.04
		IL-18	-0.50	0.04
	Myo-inositol/Cr	TNFβ	+0.51	0.04
PWM	Choline	IFN-γ	+0.58	0.03
		TNFα	+0.66	0.01
	Choline/Cr	IL-17F	+0.81	<0.01
		IL-4	+0.78	<0.01
		IL-6	+0.66	0.01
		LBP	+0.71	<0.01
		TNFβ	+0.84	<0.01
		IFN-γ	+0.58	0.03
	Myo-inositol/Cr	IL-17F	+0.81	<0.01
		IL-4	+0.78	<0.01
		IL-6	+0.66	0.01
		LBP	+0.71	<0.01
		TNFβ	+0.84	<0.01
		IFN-γ	+0.66	0.01

SUMMARY OF KEY FINDINGS

- **Inflammatory Biomarkers and Depression:** Pre-therapy hsCRP correlated with adolescent depression scores. MCP-1, IL-2, sCD163, and GM-CSF showed time-specific associations, highlighting a dynamic inflammatory link
- **Positive Associations in Pre-Therapy Metabolites and Inflammation:** Brain metabolites (choline, choline/Cr, myo-inositol, myo-inositol/Cr) in BG, MFGM, and PWM correlated with IL-17F, TNFβ, and IL-13, linking neuroinflammation to early immune activation.
- **Longitudinal Impact of iCAD on Later Biomarkers:** Pre-therapy iCAD levels predicted YKL40 at age 16, suggesting a role in later inflammation, though no links with brain metabolites were found.
- **Time to Viral Suppression:** Positively correlated with choline levels and CD8%, indicating a connection between metabolic brain markers and immune response during early treatment.

CONCLUSIONS

1. There is a dynamic interplay between immune biomarkers, brain MRS measures, and depression in PHIV adolescents.
2. Early hsCRP strongly linked to adolescent depression scores, suggesting a predictive role in mental health outcomes.
3. Regional brain metabolites: complex neuroimmune interactions, with key inflammatory markers (IL-17F, TNFβ, IFN-γ, LBP) consistently correlating with multiple metabolites.
4. Future research must integrate CSF biomarker profiling and predictive modeling to refine clinical interventions and improve mental health outcomes in PHIV.

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PAVE Pediatric Adolescent Virus Elimination
A Martin Delaney Collaboratory