Bacterial translocation of LPS is associated with lower cognitive abilities in men living with HIV receiving antiretroviral therapy

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Background

Neurocognitive disorders are still prevalent in people living with HIV, even in the era of effective anti-retroviral therapy (ART). Cognitive dysfunction arises with difficulties in maintaining adherence to treatments, trouble with concentration, attention, memory and organization, impeding quality of life. Neurocognitive disorders and increased risk of non-AIDS comorbidities have been linked with persisting inflammation in ART-treated PLWH. In addition to low levels of HIV replication and co-infections with other pathogens, damages to the gut mucosa are drivers of inflammation, despite long-term treatment. As the microbiome-gut-brain axis and the various interactions between the gut microbiome and the brain, is emerging in health and disease as a contributor to neurocognition, we assessed whether 1) markers of gut damage like intestinal fatty acid-binding protein (I-FABP) and regenerating islet-derived protein 3α (REG3α), and 2) markers of microbial translocation such as bacterial lipopolysaccharide (LPS) and fungal 1-3-β-D-Glucan (BDG), were associated with cognition in ART-treated PLWH.

Methods

80 ART-treated men living with HIV from the Brain Health Now Canadian cohort were included. Three groups of 26-27 participants were selected based on their B-CAM (computerized measure of cognition): low, intermediate, or high. Those who received antibiotics or proton pump inhibitors or anti-acids in the past 3 months were excluded (influence the gut or inflammation). Cannabis users were also excluded.

Presence of cognitive difficulties was documented using the 20-item Patient Deficit Questionnaire (PDQ), which assesses self-reported memory, attention, organization, and planning over the previous 4 weeks. A higher score is associated with more cognitive difficulties.

Baseline EDTA plasma, frozen at -80°C, was obtained for all participants. Levels of I-FABP, REG3α, and LPS were quantified by ELISA, while BDG levels were assessed using the Fungitell assay.

Table 1	Median	Interquartile range
Age	52	46-59
CD4 T cell count (Cells/µL of blood)	589	410-802
CD8 T cell count (Cells/µL of blood)	750	560-1026
CD4:CD8 ratio	0.8	0.5-1.1
HIV Viral load (copies/mL)	<50	Undetected - <50
Duration of infection (years)	13.8	8.7-23.0
Duration of treatment (years)	12	6.6-17.8
Ethnicity		
- Black	8 (10%)	
- Mixed	7 (8.75%)	
- White	51 (63.75%)	
- Other	8 (10%)	
- Missing	6 (7.5%)	
Education categories		
- High school	16 (20%)	
- College (CEGEP), technical or vocational diploma	20 (25%)	
- University (undergraduate)	29 (36.25%)	
- University post-graduate or professional degree	15 (18.75%)	
Biomarkers		
Leaky gut:		
- IFABP	965.5	659.6-1381.4
- REG3α	4302.4	2912.6-6428.2
Microbial translocation:		
- LPS	47.2	32.7-79.2
- BDG	14.5	9.0-28.0

Results

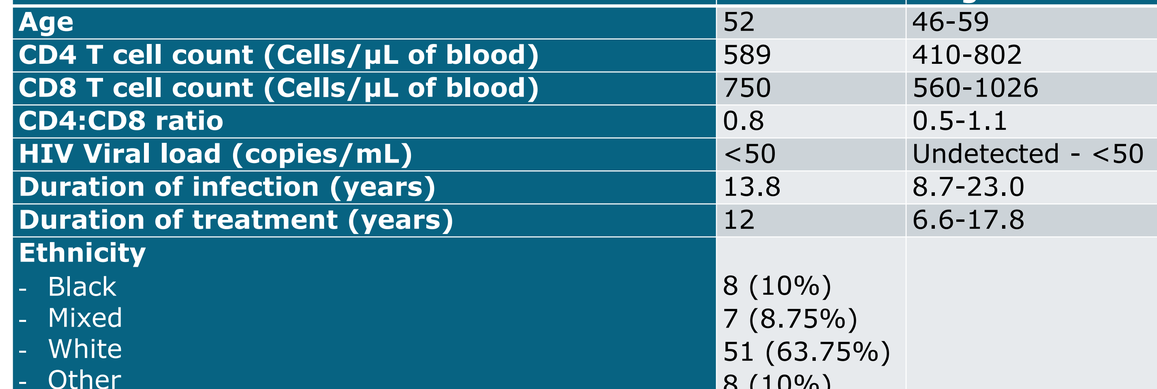

Figure 1: Participants with PDQ higher than the median levels of 26.25 had had higher plasma levels of REG3α and LPS, but not I-FABP or BDG.
Mann-Whitney's test.

PDQ *vs.* biomarker	Analysis type: Continuous	Ordinal	Binary	Spline pic	Confidence range
IFABP				Figure 2A	500 - 1500 pg/mL
REG3α				Figure 2B	1.8 - 7.5 ng/mL
LPS				Figure 3A	20 - 70 pg/mL
BDG				Figure 3B	6 - 30 pg/mL

Legend		
	Strong effect	↗ biomarker = ↗ cognitive difficulties
	Weak effect	
	No effect	
	Weak effect	↗ biomarker = ↘ cognitive difficulties
	Strong effect	

Table 1: Association between plasma levels of each biomarker and PDQ in different univariable analyses.
Moreover, age and education category had no effect on these associations (logistic regression analyses)

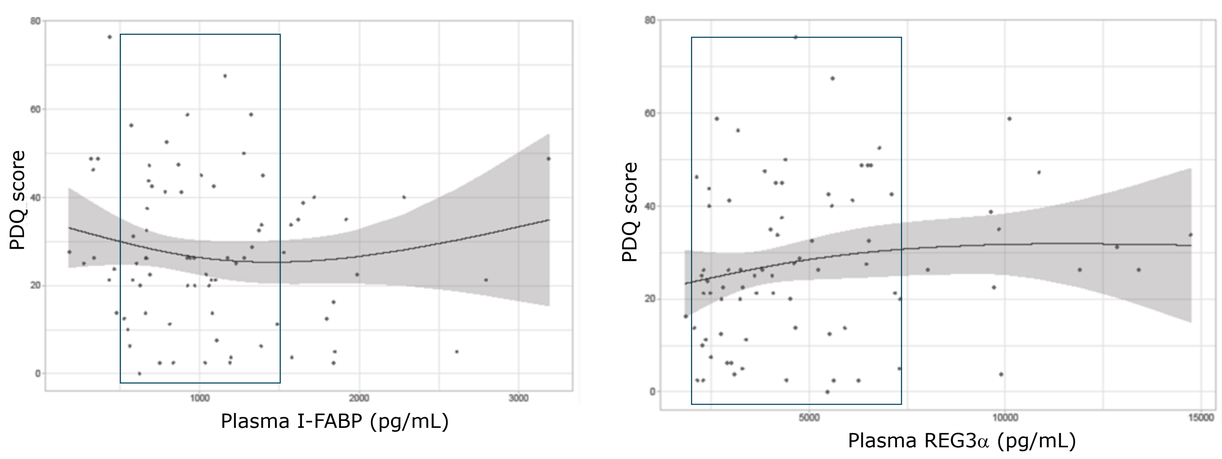

Figure 2: Spline graphs of gut damage markers *vs.* PDQ.
A. IFABP *vs.* PDQ score, B. REG3α *vs.* PDQ score.
Spline with 2 degrees of freedom are depicted. Confidence interval is shown in a blue frame.

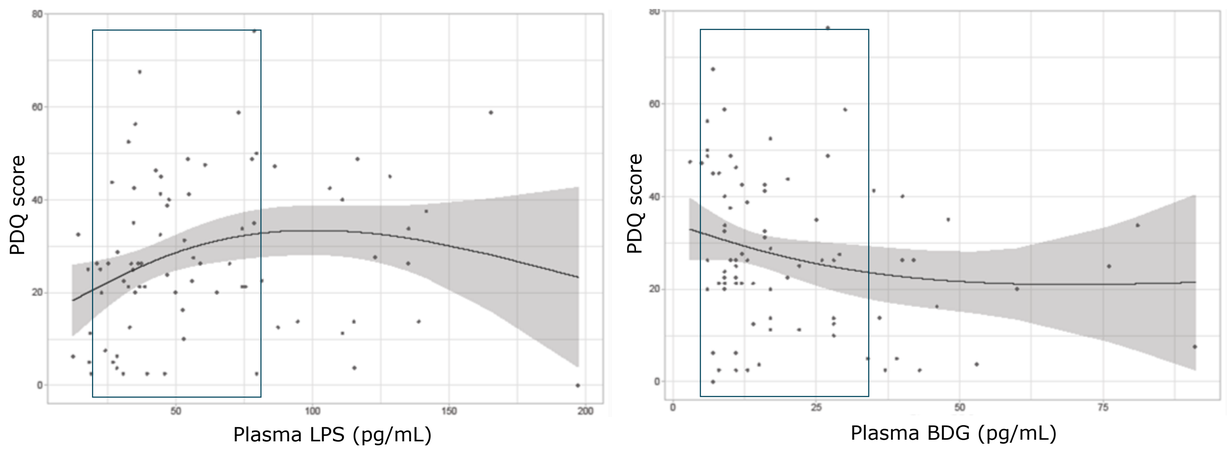

Figure 2: Spline graphs of microbial translocation markers *vs.* PDQ.
A. LPS *vs.* PDQ score, B. BDG *vs.* PDQ score.
Spline with 2 degrees of freedom are depicted. Confidence interval is shown in a blue frame.

Conclusions

Our study findings suggest that both gut permeability and microbial translocation participate in decreased cognitive function observed in some PLWH. More research is warranted to confirm the causality of this association, and its link with systemic inflammation and the gut microbiota composition. New therapeutic tools are required to reduce microbial translocation and improve gut health in PLWH, reduce the risk of developing non-AIDS comorbidities to prevent cognitive disorders in ART-treated PLWH.

Future directions

- Cluster analysis of the 4 biomarkers *vs.* PDQ.
- Comparison with cognitive function with B-CAM, a computerized measure of cognition.

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