Gut Microbiome–Cytokine Signatures and Distal Sensory Polyneuropathy in PWH

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Introduction

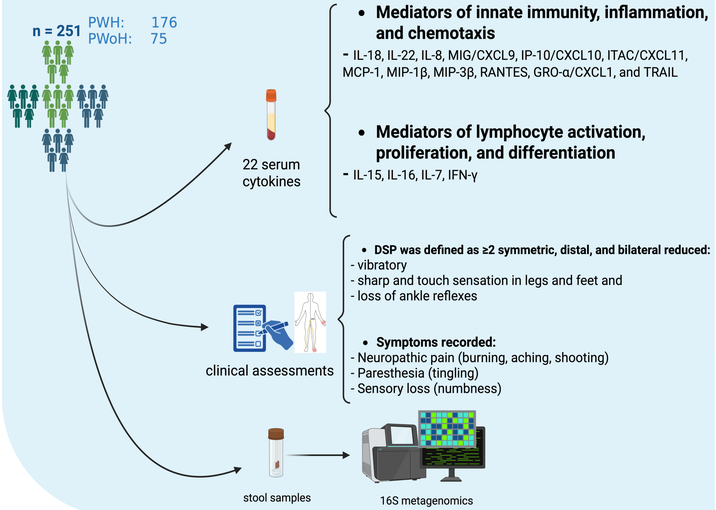
- **Persistent immune activation and chronic inflammation contribute to an elevated risk of neurological comorbidities such as distal sensory polyneuropathy (DSP) in PWH.**
- **The role of gut microbiota dysbiosis in DSP pathophysiology remains inadequately characterized due to limited studies and a lack of mechanistic understanding.**

Objectives

We investigate the interplay between gut microbiome composition, inflammatory cytokine profiles, aging, and DSP in PWH, with the objective of:

- **Identifying joint microbiome–cytokine signatures associated with DSP.**
- **Testing whether age → DSP is mediated by specific taxa**

Methods

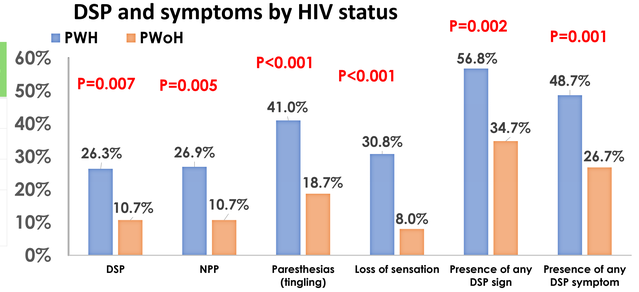


- DSP in PWH is better captured by **gut microbial composition** than by systemic cytokine profiles.
- Microbiome analyses identified a **DSP-associated compositional shift** within PWH.
- Combining clinical and microbiome-derived features yields significant discrimination of DSP status, prioritizing the microbiome as a candidate pathway for mechanistic follow-up.
- This findings underscore the importance of mechanistic studies to determine whether modifying DSP-associated microbial shifts can alter neuropathy risk or symptom burden in PWH.

Participants Demographics and Characteristics

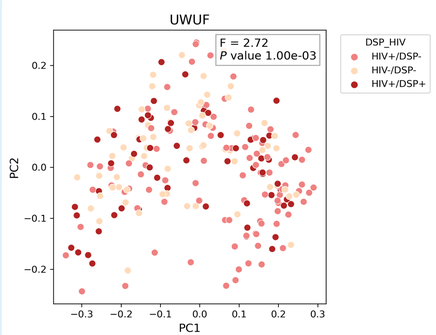
	Overall n= 251	PWH n= 163	PWoH n= 75	P-value
Age (year)	51.4 ± 13.3	51.2 ± 11.9	52.2 ± 16.2	0.37
Sex (female)	52 (20.7%)	21 (11.9%)	31 (41.3%)	<0.001
Diabetes	38 (16.0%)	27 (16.7%)	11 (14.7%)	0.84
Current CD4+ T-cells (/µL)		634.99 (±282.74)		

DSP and symptoms by HIV status



Microbiome differences associated with HIV and DSP.

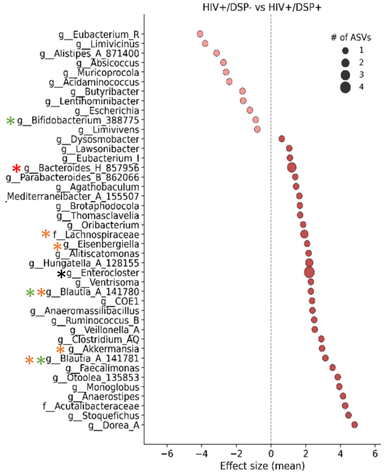
- Principal coordinates analysis (PCoA) of unweighted UniFrac (UWUF) distances showing global gut microbiome composition across three groups*.



Groups	F	Adjusted p-value
PWH/DSP- vs PWoH/DSP-	3.84	0.003
PWH/DSP+ vs PWH/DSP-	2.07	0.018
PWH/DSP+ vs PWoH/DSP-	2.20	0.012

*PERMANOVA results are shown, with pairwise comparisons summarized below the plot (F statistics and FDR-adjusted p-values).

- Diverging dot plots showing differential abundance of microbial taxa across pairwise group comparisons (PWH/DSP+ vs DSP−).
- Effect sizes (log fold changes) were estimated using BIRDMAn Bayesian differential abundance modeling adjusted for age, sex, sexual orientation, and current CD4+ T-cells count



*: ↓ butyrate/acetate-producing bacteria

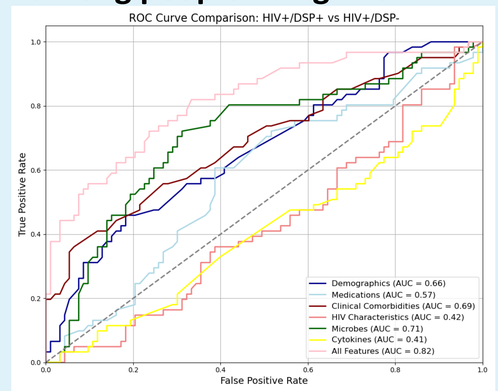
↓ mucosal dysfunction

*: Involved in CD14-LBP-TLR4 immune response

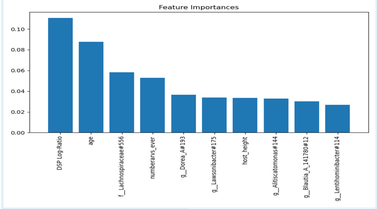
*: Progressive MS–aligned shifts.

*: linked to dysbiosis in MS, IBD, PD, autism

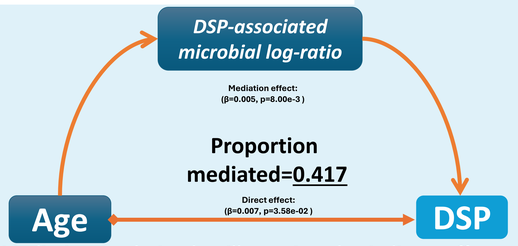
Machine learning classification of DSP among people living with HIV.



ROC curves comparing XGBoost classifier performance for distinguishing PWH with DSP+ vs DSP− individuals using different feature sets, including demographic, and clinical variables, HIV-related characteristics, microbial features, cytokines, and a combined model incorporating all features.



Feature importance rankings from the XGBoost model, highlighting the top microbial taxa contributing to DSP classification.



- **Mediation analysis also illustrating the indirect effect of age on DSP status through a DSP-associated microbial log-ratio. Path coefficients, p-values, and significance of direct and indirect indicating partial mediation by the microbiome.**
- **This points to the microbiome, as a pathway linking aging to neuropathy.**

PLAIN LANGUAGE SUMMARY

- **PWH and DSP exhibit a distinct gut microbiome signature that contributed to DSP.**
- **This pattern may partially explain the age-related DSP risk, highlighting the gut microbiome as a potential target for future preventive or symptom-focused interventions.**