# Tryptophan and Kynurenine Pathway Activation and Cognition in Virally Suppressed Women With HIV

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## BACKGROUND

- Cognitive complications persist in people with HIV (PWH) despite viral suppression
- Inflammatory cytokines and HIV proteins induce the enzyme IDO (indoleamine 2, 3-dioxygenase) to convert tryptophan (T) to kynurenine (K)
- Downstream neurotoxic metabolites arising from IDO activation may lead to cognitive complications.

- **Aim: Investigate the relationship between IDO activation and cognition in virally suppressed women with HIV (VS-WWH) and women without HIV (WWoH).**

## METHODS

- 99 VS-WWH on stable antiretroviral and 102 demographically similar WWoH from Chicago and New York sites of the Women's Interagency HIV Study
- Neuropsychological testing examined motor function, processing speed, attention/working memory, verbal fluency, verbal learning and memory, and executive function
- Plasma tryptophan and kynurenine were measured using liquid chromatography-tandem mass spectrometry
- The kynurenine-tryptophan (KT) ratio was used as a surrogate for IDO activation
- Targeted plasma monocyte-derived (sCD163, sCD14, MCP-1/CCL2) and general inflammatory markers (TNFR-II, hsCRP, hsIL-6) were measured using enzyme-linked immunosorbent assay (ELISA)
- Multivariate linear regressions were performed controlling for: days between neuropsychological testing and metabolite draw, fasting status at metabolite draw, smoking status, BMI

## RESULTS

- VS-WWH had a higher KT ratio (P<0.01) and higher sCD14 levels (P<0.05) compared to WWoH. **(Table 1)**
- There were no differences between in neurocognitive test results between VS-WWH and WWoH.
- Higher KT ratio was associated with worse fine motor domain T-scores in VS-WWH **(Figure 1)**

## Tryptophan-Kynurenine pathway activation is associated with **worse fine motor control** in virally suppressed women with HIV, independent of systemic inflammation

| Biochemical, median (IQR) | WWoH, N = 102 | VS-WWH, N = 99 | P-value[1] |
|---|---|---|---|
| **KT Ratio** | 0.654 (0.642 – 0.669) | 0.662 (0.649 – 0.684) | **0.005** |
| **Kynurenine (p.i)** | 8.90 (8.62 – 9.18) | 9.01 (8.75 – 9.26) | **0.03** |
| **Tryptophan (p.i)** | 13.62 (13.42 – 13.77) | 13.59 (13.39 – 13.76) | 0.60 |
| **sCD14 (pg/mL)** | 13.95 (13.81 – 14.19) | 14.04 (13.92 – 14.20) | **0.03** |
| **sCD163 (ng/mL)** | 5.90 (5.57 – 6.25) | 5.98 (5.62 – 6.34) | 0.22 |
| **MCP-1 (pg/mL)** | 5.18 (4.92 – 5.49) | 5.28 (4.94 – 5.56) | 0.36 |
| **TNFR2 (pg/mL)** | 7.51 (7.27 – 7.75) | 7.61 (7.39 – 7.83) | 0.06 |
| **hsIL6 (pg/mL)** | 0.61 (0.23 – 1.35) | 0.82 (0.35 – 1.27) | 0.41 |
| **hsCRP (ng/mL)** | 7.85 (6.98 – 8.73) | 7.98 (7.12 – 8.64) | 0.87 |

**Table 1. Biochemical differences between virally suppressed women with HIV (VS-WWH) and women without HIV (WWoH)**

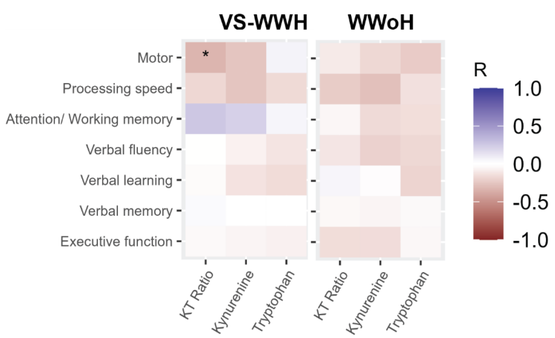


**Figure 1. Heatmaps showing Spearman's partial correlation coefficient for relationships between KT Ratio, kynurenine, and tryptophan across cognitive domains in VS-WWH and WWoH. Benjamini and Hochberg procedure was used for false discovery rate correction. * = p<0.05**

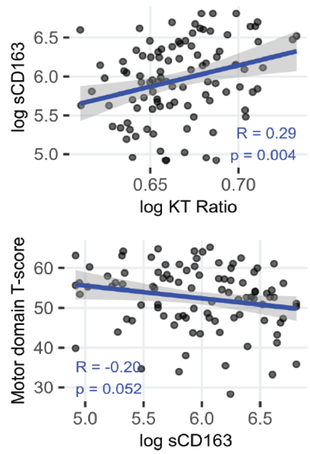


**Figure 2. Higher log sCD163 is associated with an increased log KT Ratio and worse motor function**

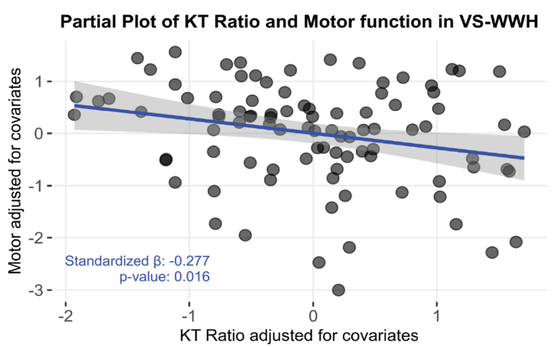


**Figure 3. Partial plot for the KT Ratio and motor domain in VS-WWH after normalization, while controlling for sCD163, CD14, and additional covariates**

## RESULTS (CONT.)

- Higher log sCD163 is associated with an increased log KT Ratio and poorer motor function (**Figure 2)**
- Greater IDO activation (higher KT ratio) is related to worse motor function in VS-WWH (r = -0.28, P<0.05). This relationship was independent of inflammatory markers. (**Figure 3)**

## CONCLUSIONS

- VS-WWH had increased IDO activation and sCD14 relative to WWoH
- Fine motor function was the only cognitive domain that correlated to IDO activation
- Although systemic inflammation may play a role, tryptophan-kynurenine pathway activation was associated with worse fine motor control in VS-WWH, independent of measured inflammatory markers

## FUTURE DIRECTIONS

- Assess IDO activation across the spectrum of motor impairments including gait and gross motor function.
- Control for individual differences in ART regimens and gut microbiota
- Sex differences in the combined MWCCS
- Investigate the use of L-Tryptophan supplementation for those with high IDO activity

## ACKNOWLEDGEMENTS

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