

2025 MQ CROI n1 1 #172

## 172 - Semaglutide Improves Cognitive Function in HIV, Effect Mediated by Decrease in Inflammation



Wed, Mar 12, 2025

07:08 PM - 07:16 PM

### Session Name

Viruses Always On My Mind: Viral Neuropathogenesis From Acute HIV to SARS-CoV-2

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### Key Terms

Adiposity, Cognitive function, HIV complications, Inflammation, Visuospatial

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### Category

General Abstract Submission

### SubCategory

(E) Neuropathogenesis and Neurologic Complications of HIV and SARS-CoV-2 Infections in Adults

### Background

People with HIV (PWH) are at higher risk for visceral adiposity and enhanced inflammation, and lower neurocognitive function when compared to controls without HIV. In a recent randomized placebo-controlled clinical trial of the GLP1 receptor agonist semaglutide, we demonstrated that PWH with lipohypertrophy had a decrease in weight, visceral adipose tissue, and in several inflammatory markers including high sensitivity C-reactive protein (hs-CRP). This study aims to investigate the effect of semaglutide on neurocognitive function and the mediation of this effect by changes in adiposity and inflammatory markers in PWH.

### Methods

This study is a randomized, double-blind, placebo-controlled phase 2b clinical trial conducted at University Hospitals of Cleveland, Ohio. We included adult PWH on ART with controlled HIV, BMI of  $\geq 25$  Kg/m<sup>2</sup>, and increased waist-to-hip ratio. Participants were randomized 1:1 to receive 32 weeks of subcutaneous Semaglutide or placebo. The Cognivue®, an FDA-approved computer-based test, was used to evaluate cognitive function at baseline and at 32 weeks. This comprehensive assessment encompassed multiple subdomains, including memory, visuospatial ability, attention, and executive function. Furthermore, a whole-body DEXA scan and a non-contrast helical CT scan were used to assess for changes in body composition, alongside the evaluation of inflammatory markers. We performed causal mediation analysis in examining association among various direct and indirect effects of semaglutide on the cognitive scores.

### Conclusion

Semaglutide has shown a beneficial impact on cognitive function in people with HIV, particularly in relation to visuospatial cognitive function. This effect appears to be mediated by the effect of the drug on inflammation.

### Results

108 participants were included (54 per arm); 62% non-white, 40% female, and median age of 53 years. Compared to placebo, PWH on semaglutide had a significant increase in visuospatial, naming/language, and delayed recall scores at 32 weeks ( $p = 0.01, 0.05, \text{ and } 0.04$ , respectively). After adjusting for sex and CD4 count, only the visuospatial score remained statistically significant ( $p=0.05$ ). The total natural direct effect (TNDE) of semaglutide maintained a positive effect on the visuospatial score while accounting for potential changes in hs-CRP levels ( $p=0.04$ ). No correlations were observed between changes in cognitive scores on semaglutide and changes in total or central adiposity.