Regulation of the Kynurenine Pathway Metabolism with the Galantamine-Memantine Combination in the Treatment of HIV-Associated Neurocognitive Disorder

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What is the Methodological Issue Being Addressed? Biomarker selection in HIV-associated neurocognitive disorder (HAND) studies is often based on small, cross-sectional, or mechanistically unrelated datasets. This limits reproducibility and makes it difficult to determine whether a biomarker is suitable for longitudinal monitoring or evaluating treatment response. We propose a tiered framework that prioritizes biomarkers according to mechanistic relevance, replication across independent human cohorts, association with neurocognitive outcomes, evidence of longitudinal or treatment-related change, analytical stability, and feasibility of repeated collection.

Introduction HAND remains common among people living with HIV despite effective antiretroviral therapy. Neuropsychological testing is essential but may be influenced by practice effects, comorbidities, participant effort, and variability in functional classification. Biomarkers may provide complementary measures of immune activation, excitotoxicity, oxidative stress, neuronal injury, and pharmacodynamic response.

The proposed design integrates kynurenine pathway, inflammatory, metabolic, and neuroimaging biomarkers within an evidence-based hierarchy. Biomarkers with replicated human evidence and direct relevance to galantamine-memantine are classified as core measures, while less replicated biomarkers are retained as exploratory measures. This approach may improve mechanistic interpretation while reducing reliance on isolated biomarker findings.

Methods Candidate biomarkers were evaluated using six criteria: mechanistic relevance to HAND; relevance to α7 nicotinic acetylcholine receptor, N-methyl-D-aspartate receptor, or kynurenine pathway signaling; replication in independent human cohorts; association with cognitive performance or HAND severity; evidence of longitudinal or treatment-related change; and analytical stability and feasibility.

Because no universal study-count or sample-size threshold defines a trial-ready biomarker, a tiered evidence framework was applied. Biomarkers supported by at least two independent human cohorts and additional longitudinal, interventional, or strong mechanistic evidence were considered core candidates. Biomarkers supported mainly by one cross-sectional cohort, a small discovery study, or untargeted analysis were categorized as exploratory.

The proposed randomized, double-blind pilot study would enroll 80 virally suppressed adults with HAND, with 40 receiving galantamine-memantine and 40 receiving placebo for 16 weeks. Biomarkers would be assessed at baseline, week 8, and week 16. Linear mixed-effects models would evaluate treatment, time, and treatment-by-time interactions. Relationships between biomarker and neurocognitive changes would be evaluated using regression analyses, with false-discovery-rate correction for secondary and exploratory outcomes.

Results The framework prioritizes the kynurenine-to-tryptophan ratio, kynurenic acid, quinolinic acid, and the quinolinic-acid-to-kynurenic-acid balance as core pharmacodynamic candidates because they reflect pathway activation, excitotoxicity, and immune dysregulation directly related to the proposed treatment mechanism. Soluble CD14, soluble CD163, and neopterin would serve as secondary markers of immune activation. N-acetylaspartate measured through magnetic resonance spectroscopy may provide complementary evidence of neuronal integrity.

Oxidative-stress markers, extracellular-vesicle profiles, and less replicated metabolic measures would remain exploratory. The projected sample would be used to estimate biomarker variability, longitudinal effect sizes, measurement feasibility, and associations with cognitive change rather than validate a surrogate endpoint.

Conclusion A tiered biomarker framework may improve HAND trial design by distinguishing replicated, mechanistically relevant biomarkers from exploratory associations. Kynurenine pathway measures are prioritized as pharmacodynamic outcomes, while inflammatory, neuroimaging, and oxidative-stress markers provide complementary information. This approach supports more reproducible biomarker selection and future validation in larger longitudinal trials.

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Keywords

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