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

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Introduction

- HAND has a reported global prevalence of 42.6% among people living with HIV and persists despite antiretroviral therapy (ART).
- The spectrum includes asymptomatic neurocognitive impairments, mild neurocognitive disorder, and HIV-associated dementia.
- No FDA-approved HAND-specific treatment is available; ART suppresses peripheral HIV but does not fully address CNS disease mechanisms.

Table 1. Biomarkers in HAND

Biomarker	Reported association in HAND
Soluble CD14 (sCD14)	Elevated; associated with cognitive impairments
Soluble CD163 (sCD163)	Elevated; associated with cognitive impairments
Cerebrospinal fluid (CSF) neopterin	Elevated; associated with cognitive impairments
Beta-2 microglobulin	Elevated; associated with cognitive impairments
Prostaglandins	Elevated in HIV-associated dementia
N-acetylaspartate (NAA)	Reduced with cognitive impairments
N-acetyl-aspartyl-glutamate	Higher levels associated with cognitive performance
Brain-derived neurotrophic factor	Higher CSF levels associated with normal cognition
S100 calcium-binding protein B	Higher CSF levels associated with normal cognition
Platelet-derived growth factor AA	Higher CSF levels associated with normal cognition
Soluble receptor for advanced glycation end products (sRAGE)	Higher CSF levels associated with normal cognition
Circulating adenosine triphosphate (ATP)	Increased
Basal-ganglia lactate	Altered; studied as a marker of HIV-associated dementia
CSF succinate	Altered; indicates mitochondrial dysfunction
Ketone bodies	Accumulated
Kynurenine/tryptophan ratio	Increased; associated with immune activation
Quinolinic acid (QUIN)	Increased
Kynurenic acid (KYNA)	Elevated
Vitamin E	Increased; predicts onset or worsening
Triglyceride CS2	Increased; predicts onset or worsening
Ceramides	Increased
Protein carbonyls	Increased
4-hydroxynonenal (4-HNE)	Increased
CSF glutathione (GSH)	Decreased
CSF extracellular vesicles	Increased
Mismatch negativity (MMN)	Altered during perceptual processing
Gamma/beta interference	Altered during motor planning
Prepulse inhibition (PPI)	Decreased with neurocognitive impairment

HAND = HIV-associated neurocognitive disorder; PLWH = people living with HIV. Associations are summarized from the manuscript review and are not established treatment-response biomarkers.

Figures

Figure 1. HIV-Associated Neurocognitive Disorders Frascati Classification

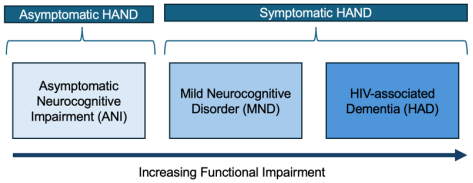


Figure 2. HIV-Associated Neurocognitive Disorder Pathogenic Positive Feedback Loop

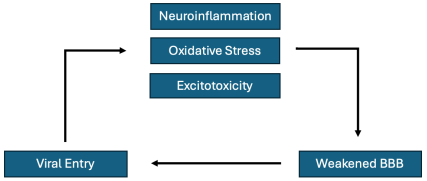


Figure 3. Regulation of the Kynurenine Pathway with the Galantamine-Memantine Combination with or without *N*-acetylcysteine

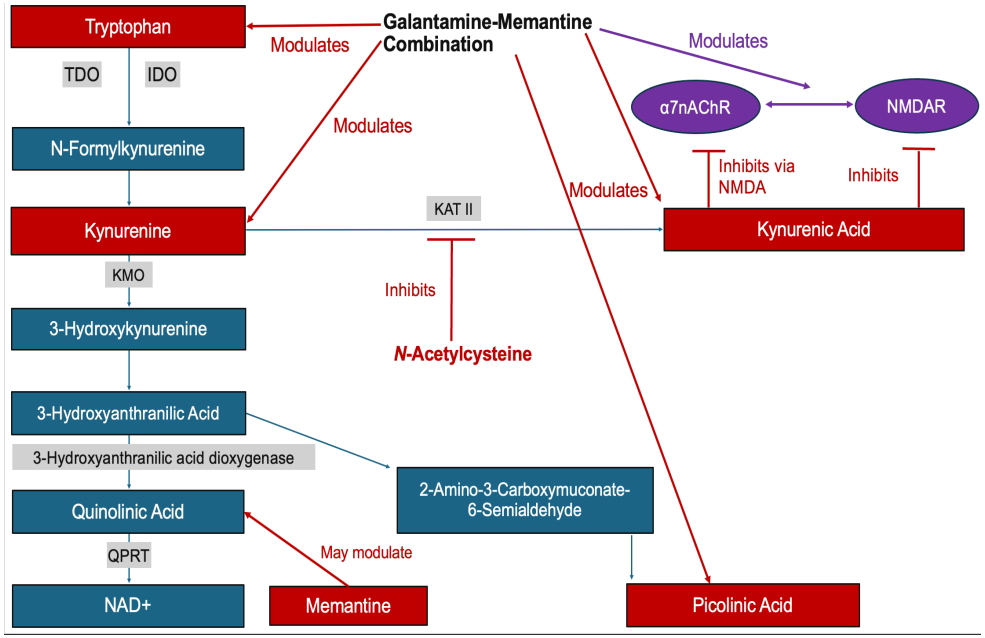
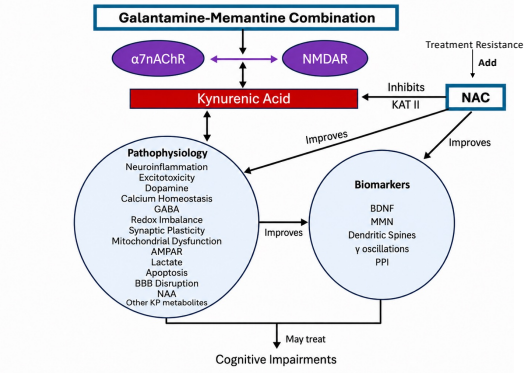


Figure 4. Galantamine-Memantine Combination Targets Pathological Mechanisms Regulated by Kynurenic Acid



Discussion

- The reviewed evidence supports a multidimensional model of HAND involving neuroinflammation, oxidative stress, mitochondrial dysfunction, excitotoxicity, and synaptic injury.
- KP imbalance may amplify these processes through altered KYNA and QUIN signaling at α7nAChR receptors and NMDA receptors.
- Galantamine and memantine engage complementary cholinergic and glutamatergic targets; NAC may add antioxidant, mitochondrial, and kynurenine aminotransferase II effects.
- Current support remains indirect because monotherapy HAND trials, preclinical models, and combination studies in other disorders cannot establish efficacy in HAND.
- Biomarker heterogeneity, comorbidities, and antiretroviral-treatment effects require prespecified control in future clinical studies.

Conclusions and Future Directions

- Galantamine–memantine with or without NAC is a testable therapeutic hypothesis, not an established treatment for HAND.
- An adequately powered RCT should evaluate cognition, safety, tolerability, and predefined KP and redox biomarkers.
- Future trials should evaluate adding NAC for patients who do not adequately respond to galantamine–memantine.
- Longitudinal analyses should determine whether biomarker change accompanies—and potentially mediates—cognitive improvement.

Selected references

Antinori et al., Neurology 2007 · Wang et al., Neurology 2020 · Bai et al., Complex Psychiatry 2021 · Schifitto et al., AIDS 2007 · Zhao et al., J Neurol 2015 · Muttikkal et al., source manuscript, 2026

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