

# HIV Associated Neurocognitive Disorders in an Antiretroviral Therapy Era

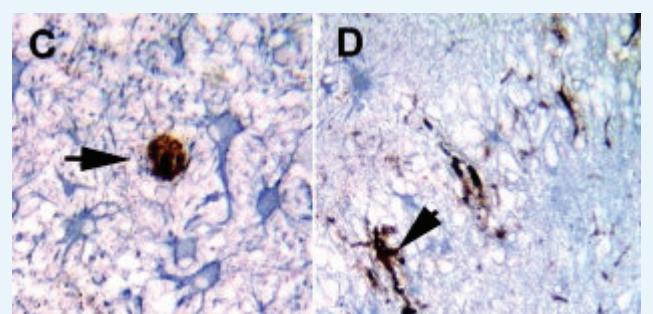
Molly Halloran, David Strayer, MD, PhD

Department of Pathology, Anatomy, and Cell Biology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA

## Introduction

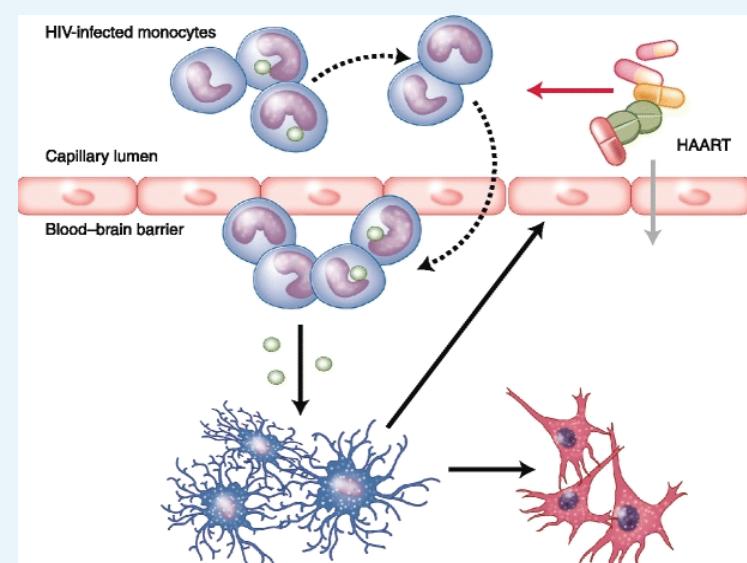
HIV emerged as a major threat to world health over 30 years ago, and while its effects on the immune system are widely known, HIV also has broad and devastating effects on the nervous system. Despite our potent antiretroviral therapies (ART), these HIV-associated neurocognitive disorders (HAND) continue to afflict HIV infected individuals. With over 33 million people infected worldwide and evidence that neurological damage can accrue in virologically well controlled individuals, HAND is a pressing challenge. Nevertheless, many questions remain unanswered about this spectrum of disorders.

## HIV Neuropathogenesis



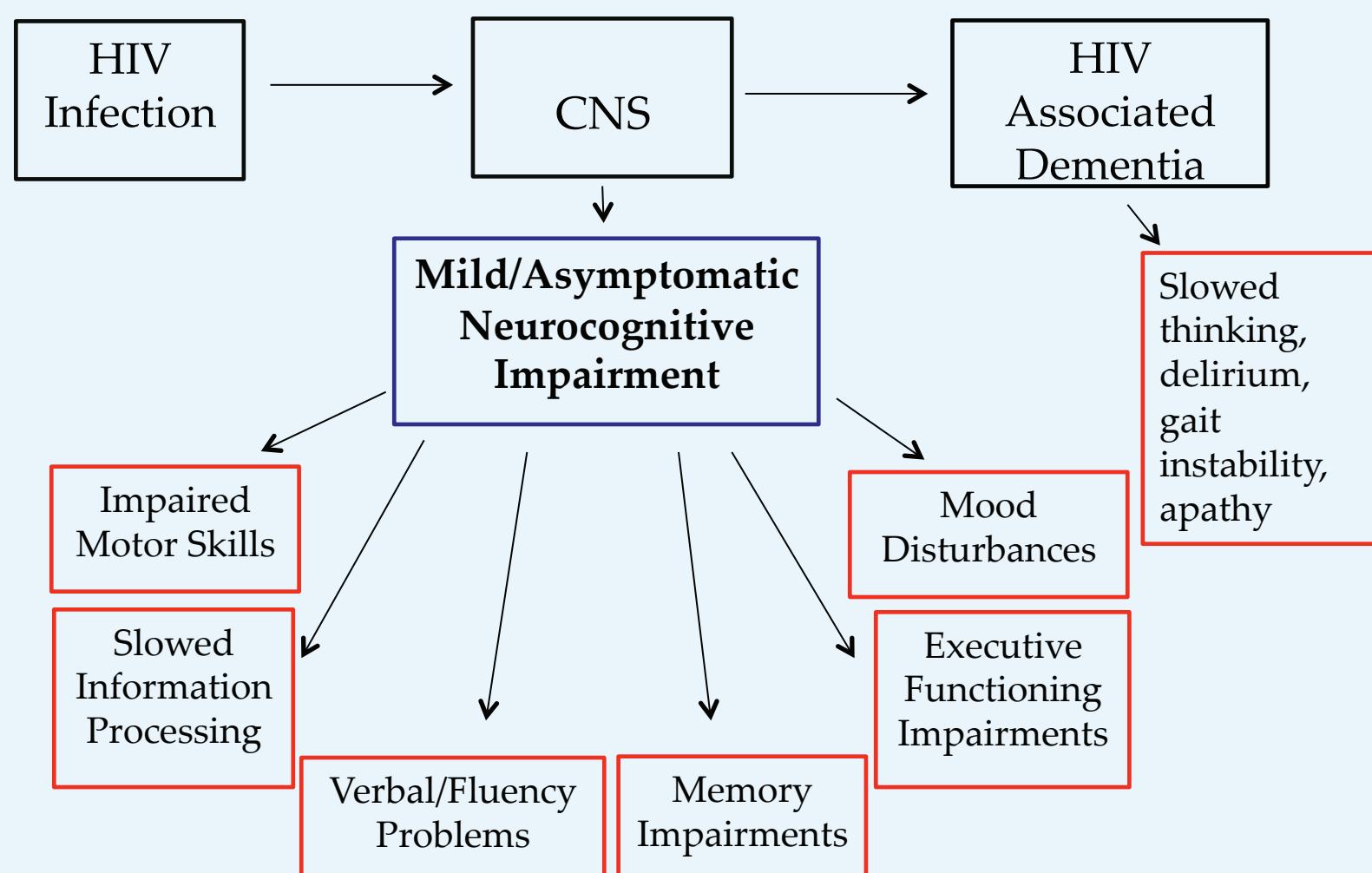
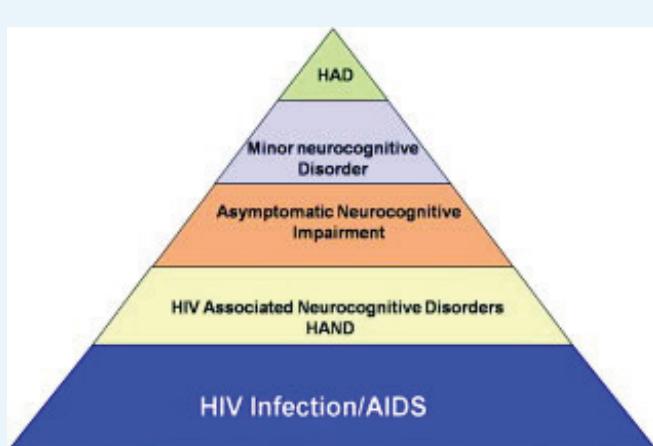
C- HIV-p24-positive macrophage  
D- HIV-infected microglia

Neuronal dysfunction is caused by cytokine dysregulation, neurotoxic soluble factors, and free radicals from activated macrophages. The CNS is a site of unchecked viral replication because most ART cannot cross the blood brain barrier. The CNS harbors a virus that is discordant from the virus in the plasma.



## HAND

HAND represents a hierarchy of progressively more severe CNS involvement. Although there has been a decrease in the most severe forms of HAND, the prevalence of milder forms are increasing. The current prevalence in HIV infected individuals is between 15-50%.



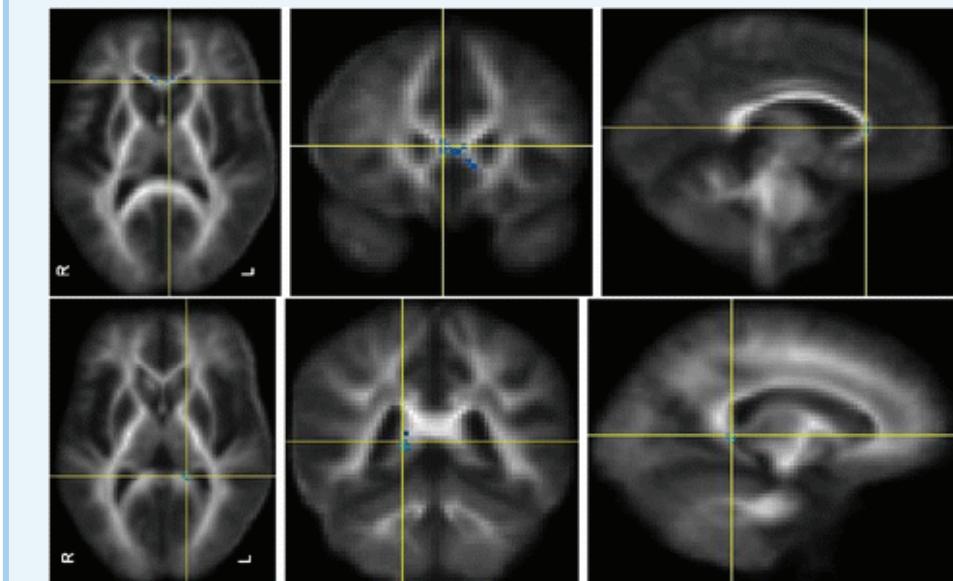
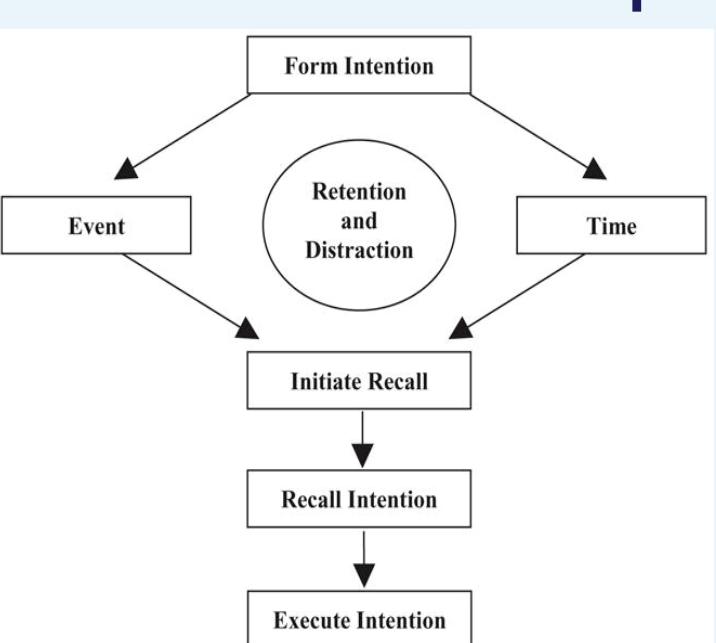
**Screening-** Current screening tests are neither sensitive nor specific for HAND. New tests are being developed to better assess the functional impairments of HAND in patients.

**Progression-** A significant amount of variation exists in the course of HAND. Patients can see static impairment, worsening of cognitive function, or even improving cognitive function.

**Treatment-** ART with greater CNS penetration exhibits more controlled CNS viral loads but no significant difference in cognitive function. Many adjuvant therapies have also been tested with no significant improvement in cognitive function.

## Prospective Memory

Prospective memory (ProM) is the ability to execute a future intention. It is largely dependent on the prefrontal-striatal circuits. HIV+ individuals exhibit deficits in the retrieval of future intentions with both time and event based cues. HIV+ individuals with prospective memory are six times more likely to be non-adherent to their ART regimen.



HIV+ individuals with poor ProM have significantly decreased white fiber tract density in the regions of the superior corona radiata, the corpus callosum, and the cingulum.

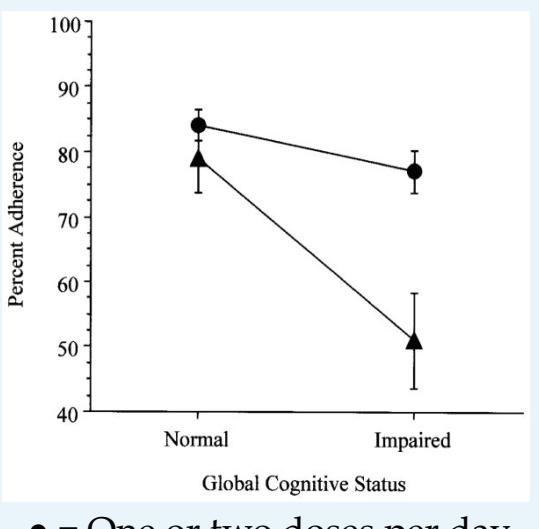
Top: HIV+ with poor prognostic memory, Bottom: HIV+ with good prognostic memory

## Speed of Information Processing

Psychomotor slowing may be among the earliest changes. It is tested through reaction time, which reflects both the cognitive processing time and time taken to physically respond, as well as through P300 latency, which represents just cognitive processing time. Overall, HIV+ individuals have increased reaction times and P300 latencies, including those who are neurologically asymptomatic. A subset of patients with more severe impairments show improved reaction time after intervention with methylphenidate, a dopamine agonist.

## Implications

Research has shown that HAND is associated with decreased medication adherence, decreased ability to perform complex daily tasks, decreased quality of life, and overall shorter survival. With increased age and length of survival being major risk factors for HAND, one of the pressing questions is whether all infected individuals with well controlled HIV infections will develop HAND over time. Some future focuses include the development of better detection and screening tools, enhanced ART delivery to the CNS, and adjuvant therapies.



## REFERENCES

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