HIV Infection of the Nervous System

Neuropsychological Factors
How Does HIV Affect the Nervous System?

- HIV easily crosses the blood-brain barrier

How Does HIV Affect the Nervous System?

- General immunosuppression can lead to:
  - Opportunistic Infections
    - Fungal (Cryptococcal Meningitis)
    - Parasitic (Toxoplasmosis)
    - Viral (Progressive Multifocal Leukoencephalopathy)
  - HIV-Related Tumors
How Does HIV Affect the Nervous System?

- Primary HIV Disease can lead to:
  - AIDS Dementia Complex (brain)
  - Vacuolar Myelopathy (spinal cord)
  - Peripheral Neuropathy (nerve)
  - Meningitis (acute and chronic)
How Does HIV Affect the Nervous System?

- HIV indirectly destroys cells in the nervous system

How Does HIV Affect the Nervous System?

- 10-15% of AIDS patients present with neurologic symptoms only.
- 35-50% of AIDS patients have neurologic symptoms during life\(^1,2\)
- 75-90% have neuropathologic abnormalities at death\(^3\)

2) McArthur J Neuroimmunol 2004; 157 : 3-10
Progression of HIV Infection of the Nervous System

<table>
<thead>
<tr>
<th>HIV neg</th>
<th>HIV positive, but otherwise asymptomatic</th>
<th>Constitutional Symptoms &amp; Severe Immunosuppression, but no OIs</th>
<th>AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic Meningitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Schematic diagram of HIV-related diseases that affect central nervous system (solid border) and peripheral nervous system (dotted border). Adapted from Johnson et al., 1988.
# Progression of HIV Infection of the Nervous System

<table>
<thead>
<tr>
<th>HIV neg</th>
<th>HIV positive, but otherwise asymptomatic</th>
<th>Constitutional Symptoms &amp; Severe Immunosuppression, but no OIs</th>
<th>AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic Meningitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV-Associated Neurocognitive Disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Schematic diagram of HIV-related diseases that affect central nervous system (solid border) and peripheral nervous system (dotted border). Adapted from Johnson et al., 1988.
HIV-associated Neurocognitive Disorders (HAND)  
(HIV-1-Associated Dementia)  
(HIV-associated Cognitive/Motor Complex)  
(HIV-associated Mild Neurocognitive Disorder)  
(Asymptomatic Neurocognitive Impairment)  
(HIV-Associated Mild Cognitive/Motor Disorder)  
(AIDS Dementia Complex)

“Patients with the AIDS dementia complex present with a variable, yet characteristic, constellation of abnormalities in cognitive, motor, and behavioral function. Perhaps the salient aspects of the disorder are the slowing and loss of precision in both mentation and motor control .... These patients often lose interest in their work as well as in their social and recreational activities.” (Price et al., 1988)
HIV-Associated Neurocognitive Disorders (HAND)

- HIV dementia is generally considered a subcortical dementia.
HIV-Associated Neurocognitive Disorders (HAND)

- HIV dementia is generally considered a subcortical dementia.
  - HIV dementia symptoms are more associated with motor slowing and loss of executive control than with language and memory disturbance.
HIV-Associated Neurocognitive Disorders (HAND)

- HIV dementia is generally considered a subcortical dementia.
  - HIV dementia symptoms are more associated with motor slowing and loss of executive control than with language and memory disturbance.
  - Later stage illness affects both cortical and subcortical regions and may affect memory.
# HIV-Associated Neurocognitive Disorders (HAND)

<table>
<thead>
<tr>
<th>Neurocognitive Impairment (Neuropsychological Testing)</th>
<th>Functional Impairment (Activities of Daily Living)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic Neurocognitive Impairment (ANI)</td>
<td>≥ Mild</td>
</tr>
<tr>
<td>Mild Neurocognitive Disorder (MND)</td>
<td>≥ Mild</td>
</tr>
<tr>
<td>HIV-Associated Dementia (HAD)</td>
<td>≥ Moderate</td>
</tr>
</tbody>
</table>


Assessment of HAND

- Behavioral Observations
Assessment of HAND

- Behavioral Observations
  - Acquired abnormality
Assessment of HAND

- Behavioral Observations
  - Acquired abnormality
  - Change in normal Activities of Daily Living
Assessment of HAND

- Behavioral Observations
  - Acquired abnormality
  - Change in normal Activities of Daily Living
  - Change in mood or normal social relationships
Assessment of HAND

- Behavioral Observations
  - Acquired abnormality
  - Change in normal Activities of Daily Living
  - Change in mood or normal social relationships
- Rule out other medical conditions
HIV-Associated Neurocognitive Disorders may share symptoms with:

- Mood disorders
- Drug and alcohol abuse
- Mania and psychosis
- Other infections and neurologic problems
- Oversedation with medications commonly given for sleep, mood problems and other disorders
Assessment of HAND

- Behavioral Observations
  - Acquired abnormality
  - Change in normal Activities of Daily Living
  - Change in mood or normal social relationships
- Rule out other medical conditions
- Neuropsychological (Cognitive) Tests
Neuropsychological Tests

- Functional Domains
  - Attention and Concentration
  - Gross and Fine Motor Skills
  - Verbal and Nonverbal Memory
  - Language Skills
  - Visuoperceptual Skills
  - Executive Skills/Higher Order Reasoning
Neuropsychological Tests

- Functional Domains Impaired in HIV
  - Attention and Concentration
  - Gross and Fine Motor Skills
  - Verbal and Nonverbal Memory
  - Language Skills
  - Visuo perceptual Skills
  - Executive Skills/Higher Order Reasoning
Neuropsychological Tests

- Mini-mental status exam lacks sensitivity (no measures of psychomotor change)
- Standard psychological measures (personality, aptitude, achievement) are helpful, but lack specificity
Core Cognitive Impairments

- Cognitive and motor slowing
  - Reaction time tests
  - Motor measures
- Poor divided attention / executive skills
  - Trail Making test
  - Stroop Color Interference
- Memory (usual in later stages)
Trail-Making Part B

Diagram showing a series of numbered circles (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13) connected with lines to form a trail.
Stroop Color Interference Test
Grooved Pegboard
Neuropsychological Assessment of HIV Dementia

- Neuropsychological tests are used to:
  - Identify specific patterns of cognitive impairment that are associated with HIV dementia.
  - Potentially identify different subtypes of HIV dementia.
  - Track the progression of cognitive changes typically seen in HIV dementia.
Progression of Untreated HIV Infection

Simplified course of untreated HIV infection; there is considerable variability across individuals.

--- CD4+ T Lymphocyte count (cells/mm³) --- HIV RNA copies per mL of plasma
Changes in Performance on Trails B Before and After HIV-1 Seroconversion
Changes in Performance on Trails B
Before and After Diagnosis of AIDS
Stage of HIV Disease and Neuropsychological Test Performance

- Decline on neuropsychological testing is closely linked to general systemic illness.
- In general, observable cognitive changes are not seen during early, medically asymptomatic, stages of HIV disease.
- Data from HIV-positive subjects with known dates of seroconversion suggest that there is no relationship between duration of HIV seropositivity and neuropsychological decline.
## Incidence and Prevalence of HIV-Associated Neurocognitive Disorders (HAND)

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>New cases of dementia occurred at a rate of 7% per year</td>
<td>Incidence of all types of primary HIV neuropsychiatric disease have decreased dramatically</td>
</tr>
<tr>
<td>15-40% of individuals developed dementia prior to death</td>
<td>Incidence of cognitive impairment has been halved and dementia is rare</td>
</tr>
<tr>
<td>Median survival after dementia was 6 months</td>
<td>With proper treatment, HIV is considered a chronic disease</td>
</tr>
</tbody>
</table>
Declines in Incidence of HIV-associated CNS Disease in the HAART Era
HAND in the Era of HAART

- Although incidence of HIV dementia has decreased dramatically, milder forms of cognitive impairment have increased.
- After over 25 years of research, the specific triggers for HAND remain unknown.
- Improved survival means that more individuals with HAND must learn to cope with the disabling effects of impaired cognition.
HAND in the Era of HAART

- Effective treatments for HAND are not yet available.
  - Individuals who are treated with HAART shortly after the first symptoms of cognitive impairment appear may show dramatic improvement.
  - Individuals who have shown symptoms of cognitive impairment for a while do not seem responsive to treatment.
HIV Neuropathogenesis

- Sustained CNS inflammation
HIV indirectly destroys cells in the nervous system

HIV Neuropathogenesis

- Sustained CNS inflammation
- Accelerated vascular disease
Brain Tissue Loss in AIDS

Most damage in brain regions controlling movement, memory, planning

Thompson Neuroimaging Laboratory, UCLA (2005)
HIV Neuropathogenesis

- Sustained CNS inflammation
- Accelerated vascular disease
- Amyloid deposition
Brain deposition of beta-amyloid is a common feature in HIV+ patients (age 31-58 years) (Green et al AIDS 2005)

- Amyloid is increased in diffuse non-neuritic plaques in HIV+ brains
- An increase in diffuse plaques suggest early aging with HIV infection and may be enough to cause cognitive impairment
Risk Modifiers

- Demographic Factors (age, education, etc.)
- Substance Abuse
- Genetic Factors
- CNS responsiveness to HAART
Demographic Risk Factors

- Individuals with less education are at greater risk
  - Brain reserve capacity
  - Socioeconomic status and access to health care
- Early studies suggested that older individuals may be at greater risk
In recent studies of HIV and aging, the best predictors of poorer cognitive functioning were markers of early cerebrovascular disease, \textit{not} HIV serostatus.

In the post-HAART era, it appears that HIV infection may not be a particularly important predictor of cognitive functioning, at least among individuals with access to medical care and appropriate medications.

Primary risk factors for cognitive impairment in older HIV-infected individuals are the same medical conditions that are associated with normal aging.

(Becker, 2009; Sacktor, 2009)
Genetic Susceptibility

- Several genetic loci have been tentatively associated with changes in cognitive functioning.
  - Genetic studies have been difficult to replicate.
  - Genetic factors associated with cognitive impairments may be similar across dementing disorders (HIV, Alzheimers, etc.).
  - Predictive power of genetic profiles has not been particularly strong.
Medical Treatments for HIV Dementia

- Does HAART penetrate the blood-brain-barrier?
  - Many types of HAART do not easily cross into the brain in laboratory studies
  - However, HIV-infected individuals may show increased permeability of the blood-brain-barrier
Medical Treatments for HIV Dementia

- High dose zidovudine (AZT) (ACTG 005)
- Nimodipine (ACTG 162; Calcium channel antagonist)
- Memantine (ACTG 301; NMDA antagonist)
- Selegiline (ACTG A5090; antioxidant/cell repair)
- Highly Active Antiretroviral Therapies (HAART)
Medical Treatments for HIV Dementia

- HAART usually reduces viral load both in the periphery and in the CNS.
- Reduction of viral load in the CNS is associated with reduced cognitive symptoms. (Ellis et al., 2003)
- Individuals with stable viral load do not show increased risk for cognitive decline, even after 5 years of monitoring. (Cole et al., 2007)
What are the Practical Implications of These Research Findings?

- Changes in brain metabolism may be present even during early stages of HIV infection.
- When viral load is adequately controlled, these changes in brain metabolism do not affect day-to-day functioning, motor skills, or higher order reasoning even though very subtle changes may appear on cognitive testing.
What are the Practical Implications of These Research Findings?

- With heightened viral load and immunosuppression, HIV may cause a potentially reversible inflammation of brain tissue.
- With sustained viral replication, HIV may cause permanent cell death.
- Even with uncontrolled viral load and immunosuppression, many people do not develop HIV dementia.
Goals of Current Research

- Identify risk factors for developing dementia
- Identify biological mechanisms that lead to cell death and dementia
- Establish effective screening tools to identify early stage dementia
- Develop medical interventions that will reverse the symptoms of dementia before permanent damage occurs