HIV Infection of the Nervous System

Neuropsychological Factors
HIV Infection of the Nervous System

- 10-15% of AIDS patients present with neurologic symptoms only (5% with dementia).
- 30-50% of AIDS patients have neurologic symptoms during life (20-30% with dementia).
- 70-90% of AIDS patients have nervous system abnormalities present at autopsy.
Nervous System Disease Associated with HIV

- Opportunistic Infections (Fungal, Parasitic, Viral)
- HIV-Related Tumors
- Primary HIV Disease
  - AIDS Dementia Complex (brain)
  - Vacuolar Myelopathy (spinal cord)
  - Peripheral Neuropathy (nerve)
  - Meningitis (acute and chronic)
HIV and the Brain

- HIV easily crosses the blood-brain barrier
- HIV is present in the brains of almost all infected individuals
HIV and the Brain

- HIV easily crosses the blood-brain barrier
- HIV is present in the brains of almost all infected individuals
- HIV directly or indirectly destroys cells in the nervous system
Progression of HIV Infection of the Nervous System

<table>
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<th>HIV positive, but otherwise asymptomatic</th>
<th>Constitutional Symptoms &amp; Severe Immunosuppression, but no OIs</th>
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<tbody>
<tr>
<td>Acute</td>
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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.
Direct Injury: 1 Cell Model

Target
Indirect Injury: 2 Cell Model

Diagram:
- **Initiator**
  - gp120
  - Neopterin
  - QUIN
  - β₂M
- **Target**
  - Toxins
Indirect Injury: 3+ Cell Model

Diagram showing the relationship between the Initiator, Amplifier, and Target cells, with various cytokines and signaling molecules indicated.
HIV and the Brain

- HIV easily crosses the blood-brain barrier
- HIV is present in the brains of almost all infected individuals
- HIV directly or indirectly destroys cells in the nervous system
- HIV causes a dementia syndrome in some individuals
HIV-Associated Cognitive/Motor Complex
(HIV-Associated Dementia)
(HIV-Associated Mild Cognitive/Motor Disorder)
(HIV-Related Encephalopathy)
(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)
Diagnostic Criteria for HIV-1 Dementia
(American Academy of Neurology, 1991)

- Acquired abnormality in attention, speed of processing, abstraction, memory, or verbal skills
- Acquired abnormality in motor function or decline in motivation or emotional control
### Progression of HIV Infection of the Nervous System

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# Progression of HIV Infection of the Nervous System

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<td>Myelopathies</td>
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<td>Inflammatory Neuropathy</td>
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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.
Incidence and Prevalence of HIV Dementia in the MACS (Prior to HAART)

- After a diagnosis of AIDS, new cases of dementia occurred at a rate of 7% per year.
- 15% of the MACS cohort developed dementia prior to death.
- Median survival after dementia was 6 months.
Estimated AIDS Deaths*, of Adults/Adolescents, by Race/Ethnicity, 1985-1999, United States

*Adjusted for reporting delays

Quarter-Year of Death

Number of Deaths

White, not Hispanic
Black, not Hispanic
Hispanic
Asian/Pacific Islander
American Indian/Alaska Native
Incidence and Prevalence of HIV Dementia in the MACS (Since HAART)

- Incidence of all types of primary HIV neuropsychiatric disease have decreased dramatically.
- Incidence of dementia has been halved.
- Survival time since diagnosis of dementia has increased dramatically.
Changes in Incidence of Cryptococcal Meningitis

Incidence rates are number per 1000 person-years.

(Sacktor et al., 2001)
Changes in Incidence of Toxoplasmosis

Incidence rates are number per 1000 person-years.

(Sacktor et al., 2001)
Changes in Incidence of HIV Dementia

Incidence rates are number per 1000 person-years.

(Sacktor et al., 2001)
HIV Dementia in the Era of HAART

• Although incidence of HIV-dementia has decreased, it continues to be a problem for many individuals.

• After 18 years of research, the specific triggers for HIV dementia remain unknown.

• Improved survival means that more individuals with dementia must learn to cope with the disabling effects of impaired cognition.
HIV Dementia in the Era of HAART

• Effective treatments for HIV dementia are not yet available.
  – Individuals who are treated with HAART shortly after the first symptoms of dementia appear may show dramatic improvement.
  – Individuals who have shown symptoms of dementia for a while do not seem responsive to treatment.
HIV Dementia in the Era of HAART

• Before we can study dementia effectively, we need specific procedures and criteria for defining what we mean by dementia.

• 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.
Assessment of HIV Dementia

- Behavioral Observations
Assessment of HIV Dementia

- Behavioral Observations
  - Acquired Abnormality
Assessment of HIV Dementia

• Behavioral Observations
  • Acquired Abnormality
  • Change in normal Activities of Daily Living
Assessment of HIV Dementia

• Behavioral Observations
  • Acquired Abnormality
  • Change in normal Activities of Daily Living
  • Change in mood or normal social relationships
Assessment of HIV Dementia

• Behavioral Observations
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• Psychological Tests
HIV-Associated Cognitive Motor Disorder shares many symptoms with:

- Depression
- Anxiety
- Drug and Alcohol Abuse
- Other infections and neurologic problems
- Oversedation with medications commonly given for sleep, mood problems and other disorders
Major Depression

![Bar chart showing Major Depression (DSM-III-R) by HIV status: HIV Negative, Asymptomatic HIV Positive, Symptomatic HIV Positive]
Assessment of HIV Dementia

• Behavioral Observations
  ▪ Acquired Abnormality
  ▪ Change in normal Activities of Daily Living
  ▪ Change in mood or normal social relationships

• Psychological Tests

• 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
  - Visuoperceptual Skills
  - Executive Skills/Higher Order Reasoning
Trail-Making Part B
Symbol Digit Modalities

KEY

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\begin{array}{ccccccc}
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1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9
\end{array}
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Stroop Color Interference Test
Neuropsychological Assessment of HIV Dementia

- Neuropsychological tests can be used to identify specific patterns of cognitive impairment that are associated with HIV dementia.
- Neuropsychological tests can be used to track the progression of cognitive changes typically seen in HIV dementia.
Models of HIV-Associated Dementia

- Progressive cognitive decline starting at time of initial infection
- Latency period followed by gradual decline
- Latency period followed by rapid decline
- Multiple latent or dormant periods and declines
Changes in Performance on Trails B Before and After HIV-1 Seroconversion

![Graph showing changes in performance on Trails B before and after HIV-1 seroconversion. The x-axis represents years before or after HIV-1 seroconversion, ranging from -0.5 to 2.5. The y-axis represents z-scores, ranging from -2 to 2. The graph compares seronegative and seroconverter groups, with the seroconverter group showing a slight decrease in performance compared to the seronegative group.](image-url)
Changes in Performance on Trails B Before and After Diagnosis of AIDS

Years Before or After Diagnosis of AIDS

-2 -1.5 -1 -0.5 AIDS 0.5 1 1.5

z-scores

-2 -1 0 1 2

Seronegative
AIDS
Cross-Sectional vs. Longitudinal Assessment

- Unless a patient is grossly demented, you cannot evaluate *decline* in cognitive functioning without serial assessments.
- Accurate diagnosis of HIV-Associated Cognitive/Motor Disorder *requires* multiple observations over at least a one month period.
- Symptoms of depression (apathy, impaired attention, motor slowing) are often misinterpreted both by patients and by health care workers as early signs of dementia.
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.
MACS Neuropsychological Study
Longitudinal Findings

• Cognitive decline most often occurs around the time of severe immunosuppression or AIDS

• Clinically significant cognitive impairment is relatively infrequent even among individuals with AIDS
What is Going on Cognitively During Earlier Stages of HIV Disease?

- Many patients continue to report changes in memory and other cognitive skills even during the asymptomatic phase of the disease.
- Very sensitive cognitive psychology measures sometimes show subtle changes during otherwise asymptomatic HIV disease.
- Functional neuroimaging suggests that some changes in brain metabolism may occur at relatively early stages of HIV disease.
$^1$H MRS abnormalities in AIDS dementia

Linda Chang, Thomas Ernst
Harbor-UCLA Medical Center
Metabolite Changes in the Frontal White matter

![Graph showing metabolite changes with ADC Stage](image)

- [CHO] (mmoles/kg) vs ADC Stage
- [MI] (mmoles/kg) vs ADC Stage

- p < 0.02
- p < 0.0001
NA and MI in Frontal WM vs. Stroop

**Correlation Coefficients:**
- Stroop Interference vs. Frontal WM [NA] (mmoles/kg): $r = 0.59$, $p = 0.02$
- Stroop Interference vs. Frontal WM [MI] (mmoles/kg): $r = 0.53$, $p = 0.01$
What are the Practical Implications of These Research Findings?

• While these findings are of interest to researchers and are suggestive of possible patterns of disease progression in the brain, keep in mind that almost all research to date suggests that there is no impairment of day-to-day functioning, motor skills, or higher order reasoning during otherwise asymptomatic HIV disease.

• Also, even during symptomatic HIV disease, the prevalence of HIV-associated cognitive disorders is relatively low.
Why do some patients insist that they are experiencing cognitive problems, even when they are otherwise relatively healthy?
Cognitive Complaints in Asymptomatic HIV Infection

- Studied 256 HIV negative and 233 medically asymptomatic HIV positive men
- Study participants completed neuropsychological testing and self-report measures of cognitive complaints (CFQ) and depression (CES-D)
Cognitive Complaints in Asymptomatic HIV Infection

- There was no association between cognitive complaints and neuropsychological test performance.
- For both HIV positive and negative subjects, there was a significant correlation between cognitive complaints and self-reported symptoms of depression.
Critical Issues to be Addressed

- **Potential Triggers/Risk Factors**: The specific triggers that lead some individuals to develop dementia while others remain cognitively healthy need to be identified.

- **Medical Treatments**: Treatments still need to be developed to reverse or delay the progression of dementia.
Potential Triggers/Risk Factors

• Individuals with less education are at greater risk
• Older individuals are at greater risk
• Individuals with lower hemoglobin before the onset of AIDS are at greater risk
• Individuals with lower body mass indices before the onset of AIDS are at greater risk
Higher Frequency of Dementia in Older HIV+ Individuals (Hawaii Aging Cohort)
Greater Severity of HIV Dementia in Older HIV+ Individuals (Hawaii Aging Cohort)

![Graph showing the greater severity of HIV dementia in older HIV+ individuals compared to younger individuals across different MSK stages.](image-url)
Potential Triggers/Risk Factors

- Potential explanatory factors
  - Brain reserve capacity?
  - Genetic susceptibility?
  - Greater CNS responsiveness to certain medications?
Mean Fasting Plasma Glucose with Confidence Intervals and Percent Comorbid Diabetes Mellitus by Diagnostic Category

Diagnostic Category

- No MC/MD or HAD
- HIV Associated MC/MD
- HIV Associated Dementia Complex

Mean Fasting Plasma Glucose (mg/dl):
- No MC/MD or HAD: 87.0
- HIV Associated MC/MD: 93.6
- HIV Associated Dementia Complex: 95.2

Percent Comorbid Diabetes Mellitus:
- No MC/MD or HAD: 4.4%
- HIV Associated MC/MD: 6.9%
- HIV Associated Dementia Complex: 25.8%
Is HIV Dementia Associated with an Increased Risk of Alzheimer’s Disease?

- Tat inhibits activity of beta amyloid degrading enzyme, neprilysin (Rempel et al, 2002)
- Tat and HIV dementia-associated neurotoxin, quinolinic acid, lead to increased beta amyloid
- CSF amyloid beta 1-42 levels decreased in HIV dementia, in same range as AD (Brew et al, 2004)
- Amyloid plaques identified in brains at higher frequency in older vs. younger AIDS patients
Apo E4 Increased in Older HIV Dementia Patients (Hawaii cohort)

<table>
<thead>
<tr>
<th></th>
<th>Younger</th>
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<th>Older</th>
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<tbody>
<tr>
<td></td>
<td>HIV Dementia</td>
<td>No Dementia</td>
<td>HIV Dementia</td>
<td>No Dementia</td>
</tr>
<tr>
<td>No Apo E4 allele</td>
<td>83.3%</td>
<td>65.8%</td>
<td>60.0%</td>
<td>79.2%</td>
</tr>
<tr>
<td>At least one Apo E4 allele</td>
<td>16.7%</td>
<td>34.3%</td>
<td>40.0%</td>
<td>20.8%</td>
</tr>
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</table>
The Corpus Callosum is abnormally thin in AIDS suggesting altered Cortical Structure.
HIV infected cell

toxins

Free radicals

Stimulate HIV replication

Damage to cellular organelles

Apoptosis

Free radical scavengers:
- Estradiol
- Plant estrogens
- Vitamin E
- Thioetic acid

Nitrosoglutathione
N-Acetyl Cysteine
Selenium

GSH
GSSG
GSH Peroxidase

OH·
O₂⁻
ONOO⁻
Estrogen

Increased transcription of anti-apoptotic genes

integrins

matrix proteins

αβγ

GSK-3

Cox-1 and -2

Cox inhibitors including indomethacin

Glutamate
Quinolinate
Tat

gp120

TNF

EAA receptors

NMDA receptor antagonists

MMP inhibitors

G protein-coupled receptors include:

CXCR4

CCR5

PAF receptor

EPs (prostaglandin E receptors)

MMPs

PAF and chemokine receptor antagonists

(1) heterotrimeric G protein complex

Calcium

A.A.

PGE

Intemembrane space

Cytosol

Mitochondrion

F0F1ATPase molecule

Active site

H+ to H+

Increased transcription of anti-apoptotic genes

GSK-3 inhibitors including lithium and valproate

Tat gp120

TNF

SDF

PAF

PGE

TNF

SDF
Medical Treatments for HIV Dementia

- **High dose zidovudine (AZT)** (ACTG 005)
- **Nimodipine** (ACTG 162; Calcium channel antagonist)
- **Memantine** (ACTG 301; NMDA antagonist)
- **Ritalin** (psychostimulant)
- **Selegilene** (ACTG A5090; antioxidant/cell repair)
- **Highly Active Antiretroviral Therapies (HAART)**
Assessment of Treatment Effects

- Behavioral Observation
- Psychological Tests
- Neuropsychological Tests (current gold standard)
- Functional Neuroimaging
  - Changes in Brain Metabolites secondary to Treatment
  - Changes in Brain Function while engaged in Cognitive Tests
HAART and Changes in Cognitive Functioning

- Studied 51 men in the MACS with cognitive impairment who were just initiating HAART
- Men were classified as “responders” or “non-responders”
  - Responders = undetectable viral load within one year of starting HAART (n=30)
  - Non-responders = viral load still detectable during first year of HAART (n=21)
HAART and Changes in Cognitive Functioning

- Viral load responders were significantly more likely to show improvement on cognitive measures (Trail-Making, Symbol Digit) relative to non-responders.
HAART and Changes in Cognitive Functioning

Cognitive Changes Over One Year

- Trail-Making
- Symbol Digit

Viral load Responder  Non-Responder

Change in z-score

0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0

Trail-Making  Symbol Digit
Medical Treatments for HIV Dementia

• Method of action of HAART is not understood
  ▪ Reduced systemic viral load?
  ▪ Reduced brain viral load?
  ▪ Disruption of release of neurotoxins?

• 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

- Regardless of the mechanism, HAART usually reduces viral load both in the periphery and in the CNS.
- Reduction of viral load in the periphery is correlated with reduced cognitive symptoms, though this is probably because it also is correlated with reduced viral load in the CNS. (Ellis et al., 2003).
- Reduction of viral load in the CNS is associated with reduced cognitive symptoms.
Goals of Current Research

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