HIV in the Brain
MANAGING COMORBIDITIES IN PATIENTS WITH HIV

Shibani S. Mukerji MD, PhD
Massachusetts General Hospital, Division of Immunologic, Inflammatory and Infectious Neurological Diseases
Dana-Farber Cancer Institute, Department of Cancer Immunology and Virology
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Disclosure

• No financial disclosures
The Majority of People Living with HIV Infection In the US Are Over Age 50 Years

Source: Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, Sexual Transmitted Diseases and Tuberculosis Prevention, Centers for Disease Control and Prevention.
HIV Infection Entry Into CNS Prior to ARV

Brain

- HIV-1 Proteins (gp120, tat)
- Neurotoxic products (free radicals, oxidative stress)
- Neopterin
- Microglia
- Astrocyte
- Pro-inflammatory signals
- Blood Brain Barrier Breakdown

Blood

- Tcell
- Monocyte
- HIV virons or fragments

Multiple Anatomical Compartments Exist for CNS HIV Infection

HIV Enters the Central Nervous System Early in Acute Infection

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Neuroinflammation and Neuroanatomical Changes Occur in Acute HIV Infection

Neuroinflammation Persists in Chronic HIV Infection Despite ARV

Positron emission tomography (PET): Abnormal brain uptake of ligand targeting activated microglia vs. HIV-controls (mean age 40 yrs; ARV 4 years)

CSF: Elevated Neopterin levels and abnormal intrathecal humoral responses in CSF despite ARV (mean age 51 years; ARV 4.8yrs)

Landscape of Cognitive Impairment in HIV Infection has Changed Dramatically with ARV

HAD: HIV associated dementia
MND: Mild neurocognitive disorder
ANI: Asymptomatic neurocognitive impairment

Therapeutic paradox: ARV has reduced prevalence of most severe manifestation of HAND (dementia) but not less severe manifestations. HAND may continue to affect daily functions, quality of life, ART adherence.


Slide courtesy of Raj Gandhi
Clinical Spectrum of HIV-Associated Neurocognitive Disorders (HAND)

<table>
<thead>
<tr>
<th></th>
<th>Pre-existing Cause &amp; Delirium Absent</th>
<th>Acquired Impairment in ≥ 2 Cognitive Domains</th>
<th>Interferes with Daily Functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic Neurocognitive Impairment (ANI)</td>
<td>✔</td>
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<tr>
<td>Mild Neurocognitive Disorder (MND)</td>
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<td>HIV-Associated Dementia (HAD)</td>
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Cognitive Functioning Across the Lifespan In The General Population

Cognitive Ability (Standard Deviations)

Processing Speed
Short-Term Memory
Long-Term Memory
Working Memory
Verbal Knowledge

Age Groups

Adapted from Park et al., Visuospatial and Verbal Memory Across the Adult Lifespan, Psychol & Aging 17:299-320, 2002
Key Questions Regarding the Relationship of HIV Infection and Age to Cognitive Function

Earlier onset cognitive decline

Interaction with other forms of dementia
The Challenge: New Diagnoses Among Older People Living with HIV Infection Is Population At Risk

40% had late stage infection at HIV diagnosis

Source: Division of HIV/AIDS Prevention, National Center for HIV/AIDS, Viral Hepatitis, Sexual Transmitted Diseases and Tuberculosis Prevention, Centers for Disease Control and Prevention.
Older People Living with HIV Infection Is Population At Risk for Cognitive Impairment

Neurocognitive Testing: The odds of neurocognitive impairment increased by 20% every decade of life in virologically suppressed PLWH who were ART adherent at 97% of visits over 2 years (median age 38 yrs).

Early ARV Treatment

**CSF:** Early ART resulted in lower IL-6 and TNF-a levels but did not differ for other soluble inflammatory markers (early ART [<4mo EDI] vs late ARV [>14mo EDI])

**CSF:** Predicted higher percentage of viral diversity with longer time to ARV in CSF but not PBMCs

**Neurocognitive Testing:** Early ART resulted in subtle improvement in some cognitive test. Those with impaired baseline cognitive function had higher CSF HIV viral load and did not reverse with early ART (Mean age 28, EDI 19 days, CD4 411)
**Neurocognitive Studies:** Among older (>50 years old) HIV+ adults compared to HIV- controls, tobacco use and diabetes was associated with worse cognitive scores (mean age 55 years).

In longitudinal studies, elevated total cholesterol predicted increased rate of cognitive decline among HIV+ adults (median age 51 years).

Nakamoto, Beau K., et al. *Journal of acquired immune deficiency syndromes* 57.3; Mukerji, Shibani, et al. *Clinical Infectious Diseases* 63.8
ARV drugs have variable distribution into the CNS and may contribute to neuropathology.

## CNS Penetration Effectiveness Score (CPE)

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The relationship between CNS penetration scores and neurological outcomes remain unclear

**CSF:** Median CSF concentrations of PIs are up to 100 fold lower than plasma concentrations event with ritonavir boosting. For Atazanavir, CSF concentrations may not consistently exceed wide-type IC$_{50}$.

**Neurocognitive Testing:** Some studies have shown that individuals with high CPE scores (≥ 9) had better cognitive scores and decreased odds of impairment (left). In contrast, other studies have shown that higher CPE scores are associated with increased risk of HIV dementia (right).

Persistent CNS HIV on ARV with Plasma Viral Suppression: CSF ‘Escape’

Mukerji., et al. Journal of acquired immune deficiency syndromes 75.2 (2017): 246
Symptomatic CNS HIV on ARV with Plasma Viral Suppression: CSF ‘Escape’

Cognitive impairment
Difficulty walking
Tremor
Visual Changes

CSF Genotype
PI: I13V, K20R, M36I, I54V, L63P, V82A

3TC*
ABC*
LPV/r**

Current First-Line Antiretroviral Regimens and Neurological Considerations

- **Tenofovir-FTC**
  - Good CSF concentration
  - Disadvantage: Less well tolerated than other agents

- **Darunavir/ritonavir**
  - Good CSF concentration

- **Raltegravir**
  - Disadvantage: twice daily (other agents are once daily)

- **Elvitegravir/cobi**
  - No CSF pharmacokinetic data

- **Dolutegravir**
  - Good CSF concentration
  - Once daily
  - Well tolerated

- **Abacavir-3TC**
  - No CSF abacavir pharmacokinetic data with daily dosing

Take Home Points

• HIV enters the central nervous system early
  • CNS has multiple anatomical compartments
  • CSF is one representative biofluid

• Neuroinflammation is established early in HIV infection and persists in chronic infection despite ART

• Neurological Cognitive Impairment is Common Among HIV infected Individuals on ART and Increases with Age

• Metabolic and Cardiovascular Disease Risk Factors are Targets to Impact Cognitive Function

• ART does not equally penetrate all tissue compartments
  • CSF resistance may be considered in patients with new neurological symptoms