**Clinical case:** I saw a 54-year-old patient in clinic last week who was complaining of memory impairment for at least 1 year. He has been positive for 15 years and virologically suppressed for over a decade. Comorbidities include mild depression treated with sertraline, hypertension, and a history of meth use.

**Disclosures**

- I have nothing to disclose.
Multiple mechanisms likely contribute to CNS injury and cognitive impairment in HIV

CNS injury early in infection not reversed by ART
Persistent, compartmentalized CNS infection
Ongoing CNS immune activation
Inflammation and immune activation -> heightened vascular disease

Inadequate antiretroviral exposure or toxicity within CNS
Neurodegeneration of aging
Co-morbidities (substance abuse, mood disorders, co-infections)

Resulting in CNS inflammation, immune activation and morphologic changes

Elevated CSF markers of macrophage and lymphocyte activation present in primary HIV infection (median 2.5 months from infection) and reduced putaminal brain volumes (median 3.33 months from infection)

CNS injury persists despite initiation of ART and virologic suppression

Even after achieving virologic suppression on ART, markers of immune activation and inflammation are persistently elevated compared with uninfected controls
Initiation of ART early in infection may mitigate inflammatory changes in the CNS

Evidence of progressive inflammation and gliosis present by MRS early in infection but attenuated after initiation of ART

But may not be adequate to prevent cognitive impairment

*Cognitive performance improved across the board after initiation of ART in acute infection, but only improvement in 1 test was significantly greater than controls

*Of 8 participants with evidence of cognitive impairment at baseline, none improved after initiating ART

The majority of persons living with HIV in the US are >50 years of age

The Aging of the HIV Epidemic in the US

CDC Surveillance Data

Aging HIV population at greater risk of cognitive impairment

After adjusting for expected effects of age using normative controls and other variables, odds of cognitive impairment increased by 20% per decade of advancing age
Neurodegenerative diseases (e.g., Alzheimer’s, Parkinson’s)


And cerebrovascular disease

In ALLRT cohort, rates of stroke higher with each decade of advancing age.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No. of strokes</th>
<th>Person-years</th>
<th>Rate (per 1000 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>54</td>
<td>32,023</td>
<td>1.69</td>
</tr>
<tr>
<td>45-49</td>
<td>3</td>
<td>12,780</td>
<td>0.23</td>
</tr>
<tr>
<td>50-59</td>
<td>17</td>
<td>11,396</td>
<td>1.49</td>
</tr>
<tr>
<td>&gt;60</td>
<td>20</td>
<td>5,954</td>
<td>3.36</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>1,893</td>
<td>7.39</td>
</tr>
</tbody>
</table>

Chow et al. CROI 2016, manuscript under review

In ALLRT cohort, rates of stroke higher with each decade of advancing age.

Cerebrovascular risk factors are associated with worse cognitive function

In HAILO cohort, HDL >60 mg/dL ↓ odds of cognitive impairment by 45% (p=0.004)


Greater burden of cerebral white matter disease in HIV associated with worse cognitive function

*ART-treated PLWH have greater burden of cerebrovascular disease compared with HIV-uninfected counterparts, which correlated with cognitive impairment

*White matter hyperintensities mediate association between HIV and cognitive impairment

Clinical case: He has been doing well on TDF/FTC/EVG/COBI for the past few years with excellent adherence. Would you recommend changing his ARVs to a regimen with better CNS penetration?

Penetration of ARVs into CNS is highly variable

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Zidovudine</th>
<th>Abacavir</th>
<th>Didanosine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside Reverse Transcriptase Inhibitors</td>
<td>Lamivudine</td>
<td>Emtricitabine</td>
<td>Lamivudine</td>
<td>Emtricitabine</td>
</tr>
<tr>
<td>Nonnucleoside Reverse Transcriptase Inhibitors</td>
<td>Nevirapine</td>
<td>Delavirdine</td>
<td>Efavirenz</td>
<td>Etuvirine</td>
</tr>
<tr>
<td>Protease Inhibitors</td>
<td>Indinavir</td>
<td>Darunavir</td>
<td>Atazanavir</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Entry/Fusion Inhibitors</td>
<td>Maraviroc</td>
<td>Etravirine</td>
<td>Tipranavir</td>
<td></td>
</tr>
<tr>
<td>Integrate Strand Transfer Inhibitors</td>
<td>Dolutegravir</td>
<td>Raltegravir</td>
<td>Elvitegravir</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Letendre Top Antivir Med 2011

Penetration of ARVs into CNS is highly variable

Better CNS penetration associated with virologic suppression in the CSF

The relationship between CNS penetration and cognitive impairment remains unclear

*Higher CNS penetration score correlated with lower prevalence of cognitive impairment

Mara et al. AIDS 2009; Cusini et al. JAIDS 2013

Carvalhal et al. J Neurovirol 2015
The relationship between CNS penetration and cognitive impairment remains unclear

- High CPE score (vs. low CPE score) associated with 75% higher hazard of HIV dementia (aHR 1.74, 95% CI 1.15-2.65)

RCT of CNS-targeted ARVs demonstrated no significant benefit in cognitive function

- *No significant improvement in global deficit score (lower values indicate improving performance) after 16 weeks among those who received CNS-targeted therapy

Neurotoxicity of ARVs may also impact cognitive function

- Neuropsychiatric AEs (e.g., headache, insomnia, depression/anxiety) reported with DTG use (~2-10%), significantly higher than RAL and EVG use (1-2%)
- DTG + ABC. DTG in women, and DTG in older age associated with more than twice the risk of neuropsychiatric AEs

Tolerability, potency, and efficacy remain key considerations when selecting ART for persons with cognitive impairment

- RAL CSF concentrations exceed 50% inhibitory concentrations in all
- No EVG CSF pharmacokinetic data*
- DTG CSF concentrations exceed 50% inhibitory concentrations in all
- Fewer CNS side effects than EFV
- No ABC CSF pharmacokinetic data on daily dosing

*Neuropsychiatric AEs (e.g., headache, insomnia, depression/anxiety) reported with DTG use (~2-10%), significantly higher than RAL and EVG use (1-2%)

*DTG + ABC. DTG in women, and DTG in older age associated with more than twice the risk of neuropsychiatric AEs

*No significant improvement in global deficit score (lower values indicate improving performance) after 16 weeks among those who received CNS-targeted therapy
Clinical case: His ARV regimen was changed to ABC/3TC/DTG about 6 months ago, and he is tolerating this regimen well. His memory impairment is stable but not improved. Are there other adjunctive therapies to consider?

Most treatment trials for cognitive function in HIV have not demonstrated clear benefit

- Anti-inflammatory & antioxidant agents
  - Selegiline (Schifitto et al. Neurology 2009)
  - Statins (Erlandson et al. Clin Infect Dis 2017, observational)

- Treatment intensification
  - Raltegravir (Dahl et al. J Infect Dis 2011)

- Other
  - Memantine, NMDA antagonist (Zhao et al. HIV Clin Trials 2010)
  - Nimodipine (Navia et al. Neurology 1998)

Benefit of treatment intensification during acute HIV on cognitive function

- Initiation of ART + RAL + MVC during acute HIV associated with better cognitive performance at 24 weeks but not significantly different than non-intensified treatment arm

Benefit of treatment intensification on global cognitive function

- Moderate to large effect of maraviroc intensification observed at 6 and 12 mos on global cognitive function

- 24-week cenicriviroc intensification improved global cognitive function, working memory and attention

Valcour et al, PLOS One 2015

Gates et al, AIDS 2016, Nduvo et al, CROI 2017
Paroxetine associated with improved cognitive function in a randomized, double-blind, placebo-controlled trial

*Sacktor et al. J Neurovirol 2017*

Physical activity associated with better brain integrity

*Ortega et al. J Int Neuropsychol Soc 2015*

Short aerobic exercise program intervention did not improve cognitive function

*Mcdermott et al. AIDS Care 2017*

Considerations in persons living with HIV with cognitive impairment

- Optimize ARV regimen
- Minimize polypharmacy
- Address psychiatric comorbidities (e.g., depression, substance use)
- Aggressive vascular risk factor modification: *the earlier, the better*
- Screen for and treat other comorbidities (e.g., sleep apnea, hepatitis C)
- Encourage physical, mental, social activity

*Participants randomized to paroxetine performed better on most neuropsych testing at Week 24*

*Executive function but not motor function better in physically active individuals compared with sedentary individuals across the age span*

*Physically active individuals have larger putaminal volumes compared with sedentary individuals across the age span*

*At baseline, physical activity and aerobic fitness associated with better cognitive performance.*

*No change in cognitive performance after 16-week aerobic exercise program (60% adherence)*
**Clinical case:** My patient is on TAF/FTC/EVG/COBI (CD4 900s, VL most recently undetectable but has been intermittently in the low 100-200s) and was admitted with 3 spells of altered mental status concerning for seizures.

CSF demonstrated a mild lymphocyte predominant pleocytosis, protein 95 and multiple CSF oligoclonal bands. CSF HIV viral load was positive at 12,600 copies/mL. Is this adequate to make a diagnosis of HIV CNS escape, or would you proceed to a brain biopsy?

---

### Independent viral replication (a.k.a. compartmentalization) occurs within the CNS

<table>
<thead>
<tr>
<th>Equilibrated</th>
<th>Compartmentalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub. 9001</td>
<td>308 d.p.i.</td>
</tr>
<tr>
<td>Sub. 9040</td>
<td>352 d.p.i.</td>
</tr>
<tr>
<td>Sub. 9006</td>
<td>348 d.p.i.</td>
</tr>
</tbody>
</table>

*Blood and CSF HIV populations early in infection can be equilibrated (similar) or compartmentalized (genetically distinct).*

---

### And contributes to ongoing CNS injury and a distinct viral reservoir

<table>
<thead>
<tr>
<th>Proportional to Blood</th>
<th>Equilibrated with pleocytosis</th>
<th>Clonal Amplification</th>
<th>Persistent Replication</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>CSF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood/Lymphoid</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

### HIV CNS escape is uncommon but can cause cognitive decline and other neurologic symptoms

- Dissociation between CSF and plasma virus concentration
  - Any detectable CSF virus in patients with plasma virus below level of detection
  - At least one log higher viral load in CSF in patients with low but measurable plasma viral load
- Acute to subacute cognitive decline +/- motor and sensory involvement, seizures and headache
- CSF with mild to moderate lymphocyte-predominant pleocytosis and elevated protein

---

CD8 encephalitis and CNS escape are likely on the same spectrum of HIV-related CNS injury

- 14 HIV-infected individuals with encephalitis and acute to subacute symptoms of HA, memory impairment, confusion, dizziness, seizures
- 12 of 14 patients on ART, 1 patient had recently self-discontinued ART
- 6 with preceding URI
- Of those tested, all but one had detectable CSF virus, and most CSF VL > peripheral VL

**Clinical case:** The patient’s ARV regimen was changed to ABC/3TC/DTG/DRV/r. He is clinically stable but remains encephalopathic. Would you start corticosteroids?

Evaluation and treatment of CNS escape

- Send genotype for resistance testing on CSF virus → M184V and T66A mutations
- If clinical, CSF and radiological picture consistent with CNS escape, no indication for brain biopsy
- CSF flow cytometry with at least 65% CD8+ T cells may support diagnosis
- Modify or augment ARV regimen based on 1) genotype/drug resistance testing and 2) CNS penetration

Utility of steroids in patients with CNS escape/CD8 encephalitis is unclear

- Patients treated with IV methylprednisolone 1 g daily for 5 days followed by prednisone taper
- 5 recovered without sequelae, 3 with moderate and 1 with severe deficits; 5 died within one year of onset
- Earlier initiation of steroids associated with better outcomes
Follow up and prognosis

- Repeat LP w/ contrast at ~4 weeks after modification of ARV regimen for cell count, protein, viral load (repeat as needed until CSF viral load undetectable)

- Repeat brain MRI at ~8-12 weeks after modification of ARVs
  - T2/FLAIR abnormalities stabilize and may improve but do not completely resolve
  - May also develop T1 black holes

- Speech and cognitive therapy

- Significant clinical improvement over weeks to months but often have persistent cognitive deficits

Take home points

- Cognitive impairment remains relevant issue for our patients

- CNS injury, which occurs early in infection, persists despite effective ART and virologic suppression

- Comorbidities associated with aging, including cerebrovascular disease, contribute to cognitive impairment in HIV

- The relationship between CNS penetration of ARVs and cognitive impairment is unclear

- Small studies suggest treatment intensification and paroxetine may be beneficial for cognitive impairment, though confirmatory studies are needed

- HIV CNS escape is an uncommon cause of acute/subacute cognitive decline and neurological symptoms

THANK YOU
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