Cognitive aging in the era of effective antiretrovirals

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SETTING THE STAGE
Cognitive dysfunction persists among HIV+ individuals in the era of effective antiretroviral therapies

- 5% HIV associated Dementia (HAD)
- 45% Milder forms of cognitive impairment
- 50% No cognitive impairment

ASSESSMENT
# Neuropsychological Testing

<table>
<thead>
<tr>
<th>Domain</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory/Learning</td>
<td>Hopkins Verbal Learning Test (HVLT)</td>
</tr>
<tr>
<td>Attention</td>
<td>Trail Making Test Part A</td>
</tr>
<tr>
<td></td>
<td>Letter-Number Sequence Test (LNS; Control Condition)</td>
</tr>
<tr>
<td>Working Memory</td>
<td>Letter-Number Span Task (LNS; Experimental Condition)</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Stroop Test Trial 3 (read word; inhibit color)</td>
</tr>
<tr>
<td></td>
<td>Trail Making Test Part B</td>
</tr>
<tr>
<td>Processing speed</td>
<td>Symbol Digit Modalities Test; Stroop Test Trial 2 (read) words</td>
</tr>
<tr>
<td>Fluency</td>
<td>Controlled Oral Word Association Test (COWAT)</td>
</tr>
<tr>
<td>Motor Skills</td>
<td>Grooved Pegboard</td>
</tr>
</tbody>
</table>
Verbal learning and memory

Broom
Ham
Pencil
Chicken
Notebook
Sponge
Turkey
Detergent
Scissors
Hamburger
Bleach
Eraser
Neuropsychological Testing

Fluency

little, lily, light, lark, list, lime, low

Fine Motor Skills

Trail Making Test Part A

Trail Making Test Part B

Digit Symbols

Sample Items

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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</tbody>
</table>
Testing is resource intensive in clinical settings

Neuropsychological Testing

Fluency

Trail Making Test Part A

little, lily, light, lark,

Trail Making Test Part B

Fine Motor Skills

Digit Symbols
## Mobile Devices (i.e., apps, tablets)

### Assessments

<table>
<thead>
<tr>
<th>Status</th>
<th>Assessment</th>
<th>Days Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>GREEN</td>
<td>Stroop Assessment</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Flanker Assessment</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>N-Back Assessment</td>
<td>7</td>
</tr>
<tr>
<td>HIGH</td>
<td>Task Switching Assessment</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>VSTM Assessment</td>
<td>7</td>
</tr>
</tbody>
</table>
HIV-associated neurocognitive disorders (HAND)

PATTERNS
Cognitive dysfunction persists among HIV+ individuals in the era of effective antiretroviral therapies

- No cognitive impairment: 50%
- Milder forms of cognitive impairment: 45%
- HIV associated Dementia (HAD): 5%

Cognitive aging in HIV: Heterogeneity is the rule not the exception

N=701; mean age at initial visit ~45yrs; *each outcome modelled separately using group based trajectory analysis; 16% declined on ≥1 test

Most studies on HIV-associated cognitive aging includes or focuses on:

- All or predominantly men living with HIV
- Mixed samples of virological suppressed & unsuppressed individuals
- Global measure of impairment (e.g., HAND)

Optimize cognitive phenotyping to improve:
- understanding of functional consequences
- identifying underlying pathophysiology, &
- developing more targeted interventions
Women living with HIV may be more cognitively vulnerable than men living with HIV.


858 HIV+ (429 women)  
562 HIV- (281 women)

SDMT=Symbol Digit Modalities test;  
GP=Grooved Pegboard

Cognitive impairment persists among virally suppressed women aging with HIV

Att/WM=attention/working memory; EF=executive function; VS=consistent use of cART & virally suppressed; NVS=consistent use of cART but inconsistent plasma viral suppression; Int NVS=intermittent cART use & inconsistent plasma viral suppression NVS=not virally suppressed; † Norman, J Clin Exp Neuropsychol, (2011); ***p<0.001; **p<0.01; p<0.05; Δ=group difference in slopes at p<0.05
• Heterogeneity in cognitive aging is the rule not the exception
• Women living with HIV may be more cognitively vulnerable than men living with HIV
• Cognitive impairment persists despite continued viral suppression
MECHANISMS
Cognitive systems impacted by aging with HIV

Cognitive Systems
- Declarative memory
- Attention
- Working memory
- Cognitive control
- Language

thoughts, behaviors, affect

Circuits
- HI circuitry (e.g., HI-PFC)
- Dorsal network (superior parietal, DLPFC)
- Ventral network (TPJ, VPFC, insula)
- PFC-parietal-cingulate-dorsal
- Thalamus-dorsal striatum
- Fronto-cingulo-parietal
- Inferior frontal, parietal, temporal

NIMH Research Domain Criteria (RDoC)
Cognitive systems impacted by aging with HIV

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NIMH Research Domain Criteria (RDoC)
HIV-related alterations in brain function during a declarative memory task in midlife women

**Region of interest analysis:**

A. Encoding words:

- ↓ HI activity in HIV+ vs. HIV- women
- ↓ HI activity associated with ↓ HVLT performance (r’s>0.54)

B. Recognition:

- ↑ HI activity in HIV+ vs. HIV- women
- ↑ HI activity associated with ↓ HVLT performance (r’s<-0.62)

**Whole-brain analysis:** HIV-alterations in PFC during encoding & recognition; PFC related to ↓ HVLT performance

Maki, Rubin et al., *Neurology* (2009)
Hormonal and inflammatory contributions to declarative memory dysfunction in virally suppressed midlife HIV+ women

**Mechanisms**
Hormonal & inflammatory

**Cognitive System**

**Declarative Memory**

HI circuitry (e.g., HI-PFC)

Hormonal and inflammatory contributions to declarative memory dysfunction in virally suppressed midlife HIV+ women

Mechanisms
Hormonal & inflammatory

Cognitive System

Declarative Memory

Circuits
HI circuitry (e.g., HI-PFC)

Silverman et al., Annals of the NYAS (2012)

Slide courtesy of Dr. Joan Berman
Adapted from: Williams & Veenstra, et al, 2014
Probing the HPA axis & inflammation using low dose hydrocortisone (LDH) improves learning & memory at the 4-hour time point in HIV

LDH improves performance vs. placebo

***p<0.001; **p<0.01; *p<0.05; T=0.06.

Rubin, JAIDS (2017); Rubin, AIDS (2018)
Magnitude of increase in salivary cortisol responsivity due to low dose hydrocortisone (LDH) is associated with verbal memory improvement at the 4 hour time point.

Enhanced performance with LDH vs. placebo

Degree to which LDH suppresses inflammatory activity is associated with LDH improvements in learning and memory only in HIV+ women

Immediate, rapid (30 min)

Delayed, slow (4 hours)

***p<0.01; **p<0.05; *p<0.10; immune responsivity = placebo – LDH; cognitive improvement = LDH – placebo; Positive association (blue) = greater inflammatory reduction; greater cognitive improvement

Higher region-specific microglial activation in the frontal cortex is associated with lower cognition in HIV+ virally suppressed individuals

Using $[^{11}\text{C}DPA-713$ with positron emission tomography (PET) to image translocator protein 18 KDa (TSPO), a marker of microglial activation.

Mean binding of the radiotracer

Rubin, Sacktor, Coughlin et al., AIDS (in press)
Higher monocyte-driven inflammation predicts lower cognitive performance in midlife HIV+ virally suppressed women.

Soluble markers of myeloid-specific activation (sCD14, sCD163)

- Global summary score
- Verbal Learning
- Verbal Memory
- Attention/Concentration
- Executive Function
- Psychomotor Speed
- Verbal Fluency
- Fine Motor Skills

Circles: standardized $\beta$ weight
Line: 95% CI around $\beta$

See for similar findings in mostly men
Burdo et al., *AIDS* (2013)—global, learning, executive function
Royal et al., *PLoS One* (2016)—global in women only

Imp, Rubin, Valcour et al., *J Infect Dis* (2016)
MECHANISMS

- Alterations in prefrontal-limbic function subserve the declarative memory deficit in midlife virally suppressed individuals
- HPA axis and inflammation may be a potential mechanisms driving cognitive deficits in learning/memory
PREDICTORS
PREDICTORS

- Mental Health
Prevalence of mental health disorders among 1027 WIHS midlife women living with HIV

**Lifetime**

- Any mood disorder
- Any anxiety disorder
- Any substance use disorder

**12-month**

- Any mood disorder
- Any anxiety disorder
- Any substance use disorder

CIDI=Composite International Diagnostic Interview

* National Comorbidity Survey Replication (NCS-R)
Lifetime mental health comorbidities among 1027 WIHS midlife women living with HIV

- Mood disorders: 390 (38%)
- Anxiety disorders: 633 (61%)
- Substance use disorders: 599 (58%)
- 33 (4%)
- 122 (14%)
- 153 (18%)
- 94 (11%)
- 29 (3%)

Based on numbers from Cook, et al. AIDS (2018)

CIDI=Composite International Diagnostic Interview
Perceived and post-traumatic stress are associated with decreased cognition in midlife HIV+ women.

- **p<0.001; **p<0.01; *p<0.05

**cART+<95% adherence or HIV RNA >10,000cp/ml**

Rubin et al., *AIDS* (2017)
PREDICTORS

- Mental Health
- Cardiovascular risk factors
Arterial stiffness is a risk factor for cognitive aging among WIHS women

Huck, Hanna, Rubin, et al., JAIDS (2018)
PREDICTORS

- Mental Health
- Cardiovascular risk factors
- Metabolic risk factors
HIV modulates the association of insulin resistance and attention among midlife women with HIV

Valcour, Rubin et al., JNV (2015)
PREDICTORS

• Mental Health
• Cardiovascular risk factors
• Metabolic risk factors
• Polypharmacy
Cognitive burden of common medications with anticholinergic properties among midlife women with HIV

Commonly used medications in WIHS women with anticholinergic properties:
Antidepressants: Trazodone, Paroxetine, Mirtazapine, Amitriptyline
Antipsychotics: Quetiapine, Risperidone, Olanzapine
Muscle relaxants: Baclofen, Cyclobenzaprine
Antihistimine: Loratadine, Diphenhydramine, Hydroxyzine

***p<0.001; **p<0.01; *p<0.05
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PTSD, Stress, menopause
Anxiolytic/anticonvulsants
Insulin resistance
Arterial stiffness
menopause

Non-ARV meds with anticholinergic properties

Opioids
Arterial stiffness
menopause

NIMH Research Domain Criteria (RDoC)
Summary/Conclusion

• **Assessment:**
  - Standard neuropsychological testing; app/tablet based assessments
  - Are we using the right measures?

• **Patterns:**
  - Persistent cognitive impairment despite viral suppressed in HIV
  - Considerable heterogeneity in cognitive systems impacted with age

• **Mechanisms:** example in midlife women:
  - Alterations in prefrontal-limbic function subserve declarative memory deficit in HIV
  - HPA axis and inflammation may be a potential mechanisms driving some of the mental health+cognitive deficits in declarative memory
  - Treatments targeting alterations might provide cognitive benefit in HIV+ individuals

• **Predictors:**
  - Numerous factors (mental health, cardiovascular, metabolic, polypharmacy) contribute or exacerbate HIV effects on specific cognitive systems
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