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

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

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>
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<tr>
<td>Working Memory</td>
<td>Letter-Number Span Task (LNS; Experimental Condition)</td>
</tr>
<tr>
<td></td>
<td><strong>blue, red, green</strong></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></td>
<td><strong>red, blue</strong></td>
</tr>
<tr>
<td>Fluency</td>
<td>Controlled Oral Word Association Test (COWAT)</td>
</tr>
<tr>
<td></td>
<td>Semantic Fluency</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

Digit Symbols

Trail Making Test Part A

Trail Making Test Part B
Neuropsychological Testing

Fluency

Testing is resource intensive in clinical settings

Trail Making Test Part A

Trail Making Test Part B
Mobile Devices (i.e., apps, tablets)
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

Heterogeneity
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
PATTERNS

• 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

**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

**Thoughts, behaviors, affect**

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

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

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

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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

### Effect Size (Cohen's d)

- **30-min**
- **4-hours**

<table>
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<tr>
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<th>Women Verbal learning</th>
<th>Men Verbal learning</th>
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***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.

Immediate, rapid (30 minutes) vs. Placebo: $r=0.34$, $p=0.04$

Delayed, slow (4 hours) vs. Placebo: $r=-0.10$, $p=0.58$

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)**

*Rubin, AIDS (2018)*

***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 $[^{11}C]DPA-713$ 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

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

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

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%)


CIDI=Composite International Diagnostic Interview
Rubin et al., *AIDS* (2017)

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 >10,000 cp/ml
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
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

Rubin, Bishop et al., JAIDS (2018)
Cognitive systems impacted by aging with HIV

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Non-ARV meds with anticholinergic properties

PTSD, Stress, menopause
Anxiolytic/anticonvulsants
Insulin resistance
Arterial stiffness
menopause
Opioids
Arterial stiffness

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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