HIV & Women: Neurological Issues

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Do women differ from men in their risk for neurocognitive and mood disorders?
As the US Incidence of HIV in Women Rose, Early Findings Were Mixed

- An early pilot study published of HIV+ women identified that women performed worse than men on tests of neurocognitive functioning
- A subsequent larger, prospective study found no difference

HIV+ Women Performed Worse in the Women’s Interagency Health Study

- HIV+ women had lower scores than HIV- women on individual neuropsychological tests
  - Trails A and B, Symbol Digit Modality Test
  - Worse insulin resistance was associated with worse performance on several tests

- In a separate analysis, HIV+ women had worse verbal, working, and visual memory
  - Worse bilateral hippocampal function correlated with worse episodic verbal memory

Manly et al, JCEN 2011, 33(8): 853
Valcour et al, ARHR 2012, 28(5): 447
Maki PM et al, Neurology 2009;72: 1661
Pattern of Impaired Cognitive Abilities May Differ Between Women and Men

- 122 adults who differed by HIV serostatus and sex
- HIV was associated with impairment to a similar extent in men (52%) and women (55%) but the pattern of impairment differed

Figure 2. Type of impairment. ■ Visual memory; □ Attention/Psychomotor speed; □ Abstract reasoning/Verbal intelligence; ☐ Verbal memory for texts; ☐ Verbal memory for digits and words.

Analyzed incidence and predictors of neurocognitive change over mean 35 months in 436 HIV+ adults who were assessed every 6 months

16.5% Improved
60.8% Stable
22.7% Declined

Heaton et al, Clinical Infectious Diseases 2015; 60(3):473–80
<table>
<thead>
<tr>
<th></th>
<th>Decline</th>
<th>Improvement</th>
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</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Female</td>
<td>-</td>
</tr>
<tr>
<td><strong>Ethnicity</strong>¹</td>
<td>Hispanic</td>
<td>Education</td>
</tr>
<tr>
<td><strong>ART Use</strong>¹</td>
<td>Off ART</td>
<td>Higher†</td>
</tr>
<tr>
<td><strong>Current CD4 Count</strong></td>
<td>Lower†</td>
<td>Higher†</td>
</tr>
<tr>
<td><strong>HIV RNA in Plasma</strong></td>
<td>Higher†</td>
<td>Higher†</td>
</tr>
<tr>
<td><strong>Serum Albumin</strong>¹</td>
<td>Lower†</td>
<td>Lower†</td>
</tr>
<tr>
<td><strong>Hematocrit</strong>¹</td>
<td>Lower†</td>
<td>Higher†</td>
</tr>
<tr>
<td><strong>Neuropsychiatric Comorbidities</strong>¹</td>
<td>Severe</td>
<td>Serum Hepatic AST¹</td>
</tr>
<tr>
<td><strong>Lifetime Methamphetamine Diagnosis</strong>¹</td>
<td>Present</td>
<td>Lifetime Substance Use Diagnosis</td>
</tr>
<tr>
<td><strong>Beck Depression Inventory</strong>¹</td>
<td>Higher†</td>
<td>Lifetime Major Depression Disorder¹</td>
</tr>
</tbody>
</table>

**Risk**

- Male
- Hispanic
- Off ART
- Lower CD4
- Higher HIV RNA in Plasma
- Lower Serum Albumin
- Lower Hematocrit
- Severe Neuropsychiatric Comorbidities
- Present Lifetime Methamphetamine Diagnosis
- Higher Beck Depression Inventory

**RR**

- 1.76*
- 2.35**
- 1.91**
- 1.14**
- 1.26**
- 2.36***
- 1.10***
- 2.47**
- 1.81*
- 1.03

**Risk**

- Female
- Non-Hispanic
- On ART
- Higher CD4
- Lower HIV RNA in Plasma
- Higher Serum Albumin
- Higher Hematocrit
- Mild Neuropsychiatric Comorbidities
- Absent Lifetime Methamphetamine Diagnosis
- Lower Beck Depression Inventory

**RR**

- Higher Education†
- Higher Est. IQ Before HIV¹
- Lower HIV RNA in CSF
- Lower HIV RNA in Plasma
- Lower Serum Total Protein¹
- Higher Hematocrit†
- Absent Lifetime Substance Use Diagnosis
- Absent Lifetime Major Depression Disorder¹

*p < 0.05, **p < 0.01, ***p < 0.0001
†CD4: per 100 cells; HIV RNA: per 1 log10 c/mL; Albumin, Hematocrit, Total Protein, AST: Per 1 “unit”; Beck Depression: Per 1 unit; IQ: Per 1 unit; Education: Per year; Hepatic AST: Per 1 mg/dL; Total Protein: Per 1 g/dL
¹Included in the final multivariable model
The Prevalence and Distribution of Major Depression in a National Community Sample: The National Comorbidity Survey

- National sample of 8,098 adults who were surveyed with a version of the Composite International Diagnostic Interview
- Prevalence estimate for lifetime major depression: 17.1%
- Correlates of current major depression:

<table>
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<th>Risk</th>
<th>RR</th>
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<tbody>
<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
<td>1.36*</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>&lt; 12</td>
<td>1.93*</td>
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<tr>
<td>Marital Status</td>
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<tr>
<td>Married</td>
<td>0.42*</td>
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<tr>
<td>Never Married</td>
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<td>Employment</td>
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<tr>
<td>Unemployed</td>
<td>2.54*</td>
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<tr>
<td>Homemaker</td>
<td>2.40*</td>
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*p < 0.05

Interaction of Cognitive, Mood, and Sleep Disorders in Women
Interaction of Cognitive Functioning and Mood Symptoms

- 708 HIV+ and 278 HIV- women from the WIHS
- HIV, but not menopausal stage, was associated with worse performance on all cognitive measures

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<thead>
<tr>
<th></th>
<th>Verbal Learning</th>
<th>Memory</th>
<th>Executive Function</th>
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<tbody>
<tr>
<td>HIV Serostatus</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
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<td>Depressive Symptoms</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
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<tr>
<td>Anxiety Symptoms</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.01</td>
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<td>Sleep Disturbances</td>
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<tr>
<td>HIV x Anxiety Interaction</td>
<td>p &lt; 0.001</td>
<td>-</td>
<td>-</td>
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*Anxiety was associated with worse learning only among HIV+ women

Rubin et al, Menopause 2014. 21(9): 997-1006
Also see: Giesbrecht et al, PLoS One 2014. 9(3): e89556
Why might neurocognitive and mood disorders occur more commonly in women?
Reasons for Greater Risk for Cognitive & Mood Disorders in HIV+ Women

- Social, financial and healthcare disadvantage
- Stress due to sexual violence and food insecurity
- Comorbid conditions, e.g., metabolic syndrome, drug use, depression
- Co-infections, e.g., CMV, HPV, STIs
- Differences in immune responses, inflammation, and oxidative stress
- Impact of sex hormones: Pregnancy and Menopause
- Differences in pharmacology and toxicity of ART and other drugs
Possible Biological Mechanisms of Sex-based Differences in Neurologic Disorders

- **Neuroprotective effects of estrogen**
  - Wallace et al, Synapse 2006, 59: 51-60

- **Adverse effects of insulin resistance in women**

- **Lower antioxidants in women**

- **Abnormalities in iron metabolism**
  - Kallianpur et al, CROI 2014, Abstract 489
Estrogen Protects from HIV tat and gp120-induced Cellular Injury

- Human neuroblastoma cells were coincubated with SIN-1 (3-morpholinosydnonimine) or tat and gp120, which increase oxidative stress
- Coincubation with 17β-estradiol (E2) attenuated tat- and gp120-induced oxidative stress
  » Progesterone had no effect

Wallace et al, Synapse 2006, 59: 51-60
Estrogen Therapy in Postmenopausal Women
Effects on Cognitive Function and Dementia

Hormone replacement therapy to maintain cognitive function in women with dementia (Review)

Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women
Women’s Health Initiative Memory Study

Hormone Replacement Therapy and the Risk of Dementia: The Women’s Health Initiative Memory Study

Effects of hormone therapy on cognition and mood
Anemia and Iron Metabolism in CHARTER

Unpublished CHARTER Data

Kallianpur et al, CROI 2014, Abstract 489
CMV is More Common in Women and is Linked to Cognitive Impairment

Bate et al, Clin Infect Dis 2010, 50: 1439-47

Letendre, et al. 19th CROI. 2012. Abstract 466
Women Have Different Exposure of Some Antiretrovirals Than Men

- Reviews of ART pharmacokinetics indicate that women can have higher drug exposure
- Difference exists for:
  - Zidovudine
  - Lamivudine
  - Ritonavir-Boosted PIs
- Mixed data for non-nucleoside RTIs

Effect modifiers:
- Adherence
- Diet and nutritional factors
- Nutritional status
- Concomitant treatments
- Hormonal environment
- Reproductive status
- Smoking

Ofotokun et al, Gender Medicine, 4(2):106-
Blood-Brain Barrier Permeability and ART Concentrations May Be Lower in Women

Unpublished CHARTER Data

- **Women**: $d = 0.64$, $p = 0.0005$, $n = 191$
- **Men**: $r = 0.50$, $p = 0.001$
- **Women**: $r = 0.68$, $p = 0.04$
How Can We Improve?

- Better ensure access to healthcare, social services, and food
- Protect women (and girls) from sexual violence
- Initiate ART early
- Assess and treat
  - Mood disorders
  - Metabolic syndrome
  - Abnormalities in iron metabolism
  - Co-infections
- Consider treating postmenopausal women with estrogen
- Investigate gender differences in CNS and systemic pharmaco-kinetics and consider regimen modification
- Develop normative data for women in the US and other countries
# Acknowledgements

## Study Volunteers

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<tr>
<th>UCSD HNRC</th>
<th>National Institutes of Health</th>
<th>Industry</th>
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<td>Ronald J. Ellis</td>
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<td>Igor Grant</td>
<td>...Drug Abuse</td>
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