Neurocognitive Disorder and HIV: a Clinician’s View

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Medical Director, Vanderbilt Comprehensive Care Clinic
Lee

- Lee is a 51 year old philosophy professor who has been academically very productive.
- Initially seen after diagnosis with HSV and candidal esophagitis. Tested HIV+ December 1994. PMH includes recurrent Zoster, CAD.
  - On a first visit in January 1995 it is noted: “He is not having significant problems with his memory and has no concentration problems at this point.”
  - Intake labs: CD4 count 160/8%; HIV RNA 370,990 copies/ml.
  - Due to a history of personal losses and medication intolerances, the patient does not agree to treatment of his HIV despite declining CD4 count and recurrent esophagitis. He continues limited palliative treatment of his severe esophagitis with short term treatment with acyclovir and fluconazole, long acting pain medications.
  - In July 1996 patient agrees to start ARV’s with unboosted indinavir and lamivudine.
Lee

From July 1996 through June 2005 he is relatively successful in controlling his virus with two interruptions June through August of 1999.

His CD4 count reconstitutes to a high of 513/19% (nadir 32/1%) in December 2004.

In 2000, he notes problems with reading: “I can’t seem to keep reading at the level I am used to”.

In 2003 he is seen by Neurology and the following is thought to be due to HIV dementia:

- He notes difficulty focusing and concentrating with respect to reading. Also noted problem with memorizing aural material, but not to the same extent. He finds that he ultimately memorizes material but it requires much greater effort. Similarly he finds he cannot recall remote memory as well. No problem with keeping checkbooks, watching TV or any other cognitive tasks.

- Only abnormal findings on exam is 1/5 recent memory recall with distraction. At this time, CD4 count is 434/14%, HIV RNA is less than 48.
In July 2004, Lee’s concerns about his mental abilities increase. He has to retire from academic life. “They are asking me to review books and I keep reading the same pages over and over again.”

After some discussion he agrees to a more thorough work up. He undergoes CT imaging of his brain, dementia labs and an L.P.

- CT scan: No evidence of parenchymal hemorrhage or abnormal extra-axial collection. Mild scattered white matter T2 hyperintensities are present predominantly peripherally. No mass or abnormal enhancement identified. The pituitary is normal in size. T1 hyperintensity in the basal ganglia compatible with chronic liver disease.

- Labs: normal TSH, B12, Folate, RPR.

- CSF: 8 cells, normal glucose, normal protein, HIV RNA 1238 (plasma less than 20). GT with no clinically significant resistance mutations.
Lee

- Attempts are made to design a possibly more CNS penetrant regimen and Lee agrees to saquinavir/norvir and truvada.
- His HIV RNA remains controlled for most of the time but his concentration and short term memory continue to decline.
  - “Dr. Raffanti, I am very concerned that if my mind continues to deteriorate like this, I can’t trust who I might vote for.”
- He remains on HAART until 2010 when he stops his antiretroviral treatment due to his poor quality of life and unaffordable copays.
- He dies in 2012 of a non-HIV related cause.
Lee’s Problem: HIV associated Neurocognitive Disease (HAND)

What was happening to Lee’s mind?

Could I have offered him effective treatment?

What caused his mental decline?

Are my other patients having the same problems?
Lee’s Problem: HIV associated Neurocognitive Disease (HAND)

- What is the classification of HAND?
- How common is HAND and how can it be identified?
- What factors are associated with the development of HAND?
- What treatments have been shown to be effective?
Clinical Features of Impairment

Cognition
- Memory loss
- Concentration
- Mental slowing

Behavior
- Apathy
- Depression
- Agitation, Mania

Motor
- Unsteady gait
- Poor coordination
- Tremor
HIV associated Dementia

- Progressive disabling disorder that manifests as an increase in loss of attention and concentration, significant motor slowing, and abnormal behavioral components.
- Historically in this country, this was the end-stage manifestation of many patients dying of untreated HIV.
- Imaging showed generalized atrophy, white matter changes
- Pathology showed cerebral atrophy, leukoencephalopathy, microglial nodules, and multinucleated cells with HIV antigen staining
- Early studies showed severity of symptoms related to: HIV RNA levels, but closer correlation with inflammatory markers including neopterin, $\text{b}_2$ microglobulin.
- The rapid clinical response to HAART in some patients suggested that a main component of pathogenesis was an inflammatory process.
  - There seems to be little information from early studies on HIV associated dementia that can be applied to the issues in HIV associated neurocognitive disease today.
# HIV associated Neurocognitive Disorders: Definitions

<table>
<thead>
<tr>
<th>Neurocognitive Status</th>
<th>Functional Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asymptomatic neurocognitive impairment (ANI)</strong></td>
<td>1 SD below mean in 2 cognitive domains*</td>
</tr>
<tr>
<td><strong>Mild neurocognitive disorder (MND)</strong></td>
<td>1 SD below mean in 2 cognitive domains*</td>
</tr>
<tr>
<td><strong>HIV-associated dementia (HAD)</strong></td>
<td>2 SD below mean in 2 cognitive domains*</td>
</tr>
</tbody>
</table>

Domains include: attention information processing, language, abstraction-executive, complex perceptual motor skills, memory, simple motor skills or sensory perceptual skills
HIV-Associated Neurocognitive Disorders (HAND)
Prevalence of Cognitive Diagnoses

- Lower incidence, but, no change in prevalence
- Lesser severity
- Most HAND cases are asymptomatic

Modified from Nat Rev Neurosci 2007
Lower incidence, but, no change in prevalence
Lesser severity
Most HAND cases are asymptomatic

Prevalence of Cognitive Diagnoses

200 healthy HIV infected patients, undetectable HIV (median 48 months; Questionnaires administered: 27% had cognitive complaints.

100 of these patients (50 with and 50 without cognitive complaints) underwent detailed neuropsychological testing: 74% had some neurocognitive disorder.

42% ANI
28% MND
4% HAD

(Simioni et al AIDS 2010)
Difficulties assessing NCD in HIV

- Definitions are imprecise: ANI vs. MND.
- HIV negative controls are seldom included in studies.
- Tools to assess mental status are not standardized or available for most clinicians.
- Education, geography and socio-economic status can influence evaluation.
- Aging has an impact:
  - Long term survival with HIV
  - Long term treatment for HIV
  - Chronic inflammation
  - Accumulation of co-morbidities
  - Evolution of aging
Projected Proportion of HIV Over 50+ Years Old

- San Francisco
  - 2001: 17%
  - 2002: 19%
  - 2003: 21%
  - 2004: 22%
  - 2005: 25%
  - 2006: 27%
  - 2007: 27%
  - 2008: 29%
  - 2009: 33%
  - 2010: 35%
  - 2011: 37%
  - 2012: 39%
  - 2013: 41%
  - 2014: 44%
  - 2015: 45%
  - 2016: 47%
  - 2017: 50%

- NY City
  - 2001: 17%
  - 2002: 19%
  - 2003: 21%
  - 2004: 22%
  - 2005: 25%
  - 2006: 27%
  - 2007: 27%
  - 2008: 29%
  - 2009: 33%
  - 2010: 35%
  - 2011: 37%
  - 2012: 39%
  - 2013: 41%
  - 2014: 44%
  - 2015: 45%
  - 2016: 47%
  - 2017: 50%

Projected based on 2008 CDC data

Adapted from JAMA 2013
A, Numbers of different classes of non–human immunodeficiency virus (HIV) medication, stratified by age.

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Potential age-related factors:

- Concurrent neurodegenerative disease
- APO E4

Other Factors:

- Lower educational attainment

Potential factors leading to:

- Multifactorial cumulative brain damage
- Clinical presentation of cognitive/behavioral/motor disorder

Concurrent cerebrovascular co-morbidity

Long-term exposure to ARV's

Chronic immune activation

Uncontrolled plasma and/or CSF HIV

HIV-specific factors

CPE = CNS Penetration-Effectiveness

(a) ARV toxicity
(b) poor CPE
Assessment Tools

- Dozens of neuropsychological testing methods have been developed to determine neurocognitive performance.
- Comparisons of studies is limited by the diversity of assessment tools used to measure outcomes of interest.
- Not all validated assessment tools have been evaluated in HIV infected patients.
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- Comparisons of studies is limited by the diversity of assessment tools used to measure outcomes of interest.
- Not all validated assessment tools have been evaluated in HIV infected patients.
Figure 1. Comparisons of the Frascati Criteria and Global Deficit Scores to define neurocognitive impairment in HIV.

SECTION 6: HAND DIAGNOSIS AND ELIGIBILITY DETERMINATION

HAND diagnosis and eligibility will be determined by Dr. Kevin Robertson, A5324 Co-Chair, using the neurocognitive forms completed at screening. HAND diagnosis and eligibility determination will be done following the procedure described below.

1. The following must be completed for each potential participant screened for the study:
   - Wide Range Achievement Test (WRAT-4) Reading Test
   - Hopkins Verbal Learning Test – Revised (HVLT-R)
   - Trailmaking A and B
   - Grooved Pegboard Dominant and Nondominant
   - Wechsler Adult Intelligence Scale (WAIS)-III Digit Symbol
   - WAIS-III Symbol Search
   - HVLT-R Delayed Recall/Recognition
   - Stroop Interference Task
   - Verbal (Letter and Category) Fluency
   - Neuropsychological Baseline Demographic Data CRF
   - Activities of Daily Living Interview/Questionnaire CRF
   - Beck Depression Inventory (BDI-II) CRF
   - Substance Use Self-Report CRF

2. The following worksheets must also be completed at screening:
   - A5324 Neuropsychological Test Worksheet (Appendix A)
   - A5324 Confounding Factors Worksheet (Appendix B).
Although the Frascati criteria allows better comparisons between studies, it is a cumbersome set of scores, possibly oversensitive (15-20% abnormal in healthy controls) and may not be generalizable in resource poor countries.
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   - Hopkins Verbal Learning Test
   - Trailmaking Test
   - Grooved Pegboard Test
   - Wechsler Memory Scale
   - WAIS-III
   - HVLT-R
   - Stroop Test
   - Verbal Fluency Test
   - Neuropsychological Test
   - Activities of Daily Living
   - Beck Depression Inventory
   - Substance Use Self-Report

Although the Frascati criteria allows better comparisons between studies, it is a cumbersome set of scores, possibly oversensitive (15-20% abnormal in healthy controls) and may not be generalizable in resource-poor countries.

Available tests are not practical but do allow comparison between clinical studies.

2. The following worksheets must also be completed at screening:
   - A5324 Neuropsychological Test Worksheet (Appendix A)
   - A5324 Confounding Factors Worksheet (Appendix B).
Causes of HAND

- Impact of Systemic Infection
- Role of antiretroviral therapy
- Biomarkers
- Host factors
HAND: Impact of systemic infection

- Ongoing CD4 count and HIV 1 RNA not clearly associated with NCD (multiple studies).

- Presence of detectable HIV-1 RNA associated with poorer memory scores. CD4 count and AIDS status was not associated with abnormal scores (Becker et al, Neurology 2009: MACS cohort, 428+/207- men).

- Prior AIDS diagnosis was associated with higher rates of NCI but not nadir CD4 count, HIV-1 RNA or CPE score of antiretroviral regimen (Wright et al, Neurology 2010: SMART sub-study, 292 HIV+ pts, 5 test neurocognitive battery).

- Sixty-five patients started on HAART (ATAZ/RTV +/- NRTI) followed for 96 weeks with thorough NC testing. 17% had baseline abnormalities. All patients had improved scores over time, regardless of HAART regimen. (CROI 2015)

- Early treatment has been associated with very low rate of NCD: 26 patients with early treatment were assessed for NCD with very low incidence (4%) (Evering et al CROI 2015 #446).
HAND: Impact of systemic infection.

- In THINC (the HIV Tropism, Persistence, Inflammation and Neurocognition in Therapy Initiation cohort) 38 treatment-naïve patients initiating ART with CD4 < 400 were administered neurocognitive testing and lumbar puncture (LP) at baseline. A follow-up LP was performed after 2-4 weeks on ART, and a neurocognitive follow-up was performed after 24 weeks on ART.

  - Conclusions: A greater reduction and more rapid decay of CSF HIV after ART initiation was related to greater improvement in neurocognitive functioning after initiating ART. (Robertson et al CROI 2015 #439)

- Forty untreated patients with varied CD4/HIV RNA levels and function. NCD testing as well as baseline CSF amplification and cloning of CSF viral isolates, pseudotypes to be used in entry assays into low CD4 expressing cells (macrophages). The observation of genetically distinct, viral lineages in the CSF was evidence of ongoing replication in that compartment, and these lineages were considered compartmentalized

  - Conclusions: HIV-1 replication in the CNS is strongly associated with neurocognitive impairment and the majority of subjects with evidence of ongoing HIV-1 replication in the CNS have macrophage-tropic HIV-1 in that compartment. (Joseph et al. CROI 2015 #440)
HAND: Impact of systemic infection.

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Conclusions: A greater reduction and more rapid decay of CSF HIV after ART initiation was related to greater improvement in neurocognitive functioning after initiating ART. Reduced viral load in the CNS likely reduces ongoing inflammatory processes causing injury to neurons, resulting in relatively improved neurocognition.

(Robertson et al, CROI 2015 #439)

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Conclusions: HIV-1 replication in the CNS is strongly associated with neurocognitive impairment and the majority of subjects with evidence of ongoing HIV-1 replication in the CNS have macrophage-tropic HIV-1 in that compartment. (Joseph et al, CROI 2015 #440)

- 155 untreated patients with paired CSF and plasma samples. 24 (15%) had higher HIV RNA levels in CSF than plasma. These patients had a 3 fold higher risk of HAND.

(Bai et al, CROI 2017, Abstract #357)
# HAND: Importance of CSF viral escape

<table>
<thead>
<tr>
<th>Age</th>
<th>CD4</th>
<th>Months VL&lt;50</th>
<th>Neurological symptoms</th>
<th>ARVs</th>
<th>CSF HIV RNA</th>
<th>Plasma HIV RNA</th>
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</thead>
<tbody>
<tr>
<td>50</td>
<td>592</td>
<td>36</td>
<td>Persistent headache</td>
<td>TDF/FTC/ATZr</td>
<td>12,885</td>
<td>147</td>
</tr>
<tr>
<td>49</td>
<td>190</td>
<td>11</td>
<td>Memory disorder, cerebellar ataxia</td>
<td>AZT/3TC/IDVr/T20</td>
<td>845</td>
<td>&lt;50</td>
</tr>
<tr>
<td>43</td>
<td>400</td>
<td>18</td>
<td>Cerebellar dysarthria, cerebellar ataxia</td>
<td>3TC/ABC/ATV/IDVr</td>
<td>1190</td>
<td>&lt;50</td>
</tr>
<tr>
<td>50</td>
<td>432</td>
<td>68</td>
<td>Tactile allodynia</td>
<td>TDF/FTC/fAPRr</td>
<td>870</td>
<td>78</td>
</tr>
<tr>
<td>36</td>
<td>107</td>
<td>75</td>
<td>Glasgow Coma Score of 3</td>
<td>3TC/ABC/TDF/DRVr</td>
<td>5035</td>
<td>&lt;50</td>
</tr>
<tr>
<td>47</td>
<td>631</td>
<td>64</td>
<td>Persistent Headache</td>
<td>DRVr</td>
<td>580</td>
<td>&lt;50</td>
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<tr>
<td>44</td>
<td>544</td>
<td>14</td>
<td>Memory d/o, cerebellar ataxia, pyramidal syndrome</td>
<td>FTC/ABC/ATVr</td>
<td>558</td>
<td>&lt;50</td>
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<td>53</td>
<td>360</td>
<td>12</td>
<td>Lower limb dysesthesia and hypoesthesia</td>
<td>3TC/AZT/ABC/EFV</td>
<td>1023</td>
<td>&lt;50</td>
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<tr>
<td>68</td>
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<td>12</td>
<td>Memory d/o, left lower limb dysesthesia</td>
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<td>&lt;50</td>
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<tr>
<td>68</td>
<td>534</td>
<td>18</td>
<td>Temporospatial disorientation, cerebellar ataxia</td>
<td>3TC/AZT/ATV</td>
<td>880</td>
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<tr>
<td>56</td>
<td>593</td>
<td>10</td>
<td>Memory d/o, cerebellar dysarthria</td>
<td>LPVr</td>
<td>6099</td>
<td>483</td>
</tr>
</tbody>
</table>

Canestri et al, CID 2010
Importance of CSF viral escape

- Sixty-nine neurologically asymptomatic well controlled patients.
- 10% had detectable CSF HIV RNA
- Detectable CSF HIV was associated with higher CSF neopterin levels, duration of treatment and frequency of interruptions
- (Eden et al JID 2010)
HAND: Impact of systemic infection

- Untreated HIV infection is associated with NCD. It is less clear if current or prior immune status are associated with development of NCI. Rate and duration of response to HAART may be important.

- In rare cases, CSF viral escape may explain NCD findings
HAND: Role of Antiretroviral therapy, independent of systemic infection

- Positive impact of HAART could be dependent on CNS penetration/effect.
- Negative impact of HAART could be related to drug toxicity.
# CNS Penetration Effectiveness Ranks 2010

<table>
<thead>
<tr>
<th></th>
<th>Much Above Average</th>
<th>Above Average</th>
<th>Average</th>
<th>Below Average</th>
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<tbody>
<tr>
<td><strong>NRTIs</strong></td>
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<tr>
<td>Zidovudine</td>
<td></td>
<td>Abacavir</td>
<td>Didanosine</td>
<td>Tenofovir</td>
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<td></td>
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<td>Emtricitabine</td>
<td>Lamivudine</td>
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<td></td>
<td>Stavudine</td>
<td>Zalcitabine</td>
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<tr>
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<td>Nevirapine</td>
<td>Delavirdine</td>
<td>Etravirine</td>
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<td></td>
<td>Efavirenz</td>
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<tr>
<td><strong>PIs</strong></td>
<td>Indinavir-r</td>
<td>Darunavir-r</td>
<td>Atazanavir</td>
<td>Nelfinavir</td>
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<td></td>
<td></td>
<td>Fosamprenavir-r</td>
<td>Atazanavir-r</td>
<td>Ritonavir</td>
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<tr>
<td></td>
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<td>Indinavir</td>
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<td>Saquinavir</td>
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<td>Lopinavir-r</td>
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<td>Saquinavir-r</td>
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<td></td>
<td>Tipranavir-r</td>
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<tr>
<td><strong>Entry/fusion inhibitors</strong></td>
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<tr>
<td>Maraviroc</td>
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<td>Enfuvirtide</td>
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<td><strong>Integrase inhibitors</strong></td>
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<tr>
<td>Raltegravir</td>
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*Letendre SL, Topics Antiviral Medicine 2011; 19(4):137-42*
### CNS Penetration Effectiveness Ranks 2010+

<table>
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<tr>
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<tr>
<td><strong>NNRTIs</strong></td>
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<td>Rilpivirine$^3$</td>
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<td>Darunavir-r</td>
<td>Atazanavir-r</td>
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<td>Lopinavir-r</td>
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<td><strong>Entry/fusion</strong></td>
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<td>Maraviroc</td>
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<td>inhibitors**</td>
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<td><strong>Integrase</strong></td>
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<td>Dolutegravir$^4$</td>
<td>Raltegravir</td>
<td>Elvitegravir/c</td>
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<td>inhibitors**</td>
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</tbody>
</table>

Figure 2. Left: Association of antiretroviral regimen CNS (central nervous system) Penetration-Effectiveness (CPE) score with proportion of patients with detectable HIV RNA in cerebrospinal fluid (CSF). Adapted from Letendre et al.29 Right: Proportion of patients with CSF viral load between 2 copies/mL and 50 copies/mL, according to antiretroviral regimen CPE score of ≤ 7 or > 7 (the median value). OR indicates odds ratio. Adapted from Letendre et al.31
CSF Penetration and Virologic Control
(Ellis et al, CID 2013)

- Multicenter RCT to enroll patients starting a new regimen of HAART.
- Patients were randomized to receive a regimen with a high or low CPE score.
- Accrual was poor and only 59 out of 120 patients were enrolled before study was stopped.
- Plasma and CSF HIV-1 RNA as well as NC testing were followed over time.
Lack of correlation with CPE score and CSF viral suppression.

(Ellis et al, CID 2013)
CSF Penetration and NC Function
(Ellis et al, CID 2013)
## Recent Reports Continue to Be Inconsistent

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>NP</th>
<th>Duration</th>
<th>Finding</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Ciccarelli¹</td>
<td>C-S</td>
<td>101</td>
<td>C</td>
<td>-</td>
<td>Beneficial</td>
<td>2010 version stronger than 2008 version</td>
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<td>Ciccarelli²</td>
<td>C-S</td>
<td>215</td>
<td>C</td>
<td>-</td>
<td>Beneficial</td>
<td>Adjusted CPE using GSS</td>
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<tr>
<td>Casado³</td>
<td>C-S</td>
<td>69</td>
<td>B</td>
<td>-</td>
<td>Trend toward benefit</td>
<td>Beneficial in CD4 &lt; 200</td>
</tr>
<tr>
<td>Vassallo⁴</td>
<td>L</td>
<td>96</td>
<td>C</td>
<td>22 months</td>
<td>Beneficial</td>
<td>~25% were not virologically suppressed</td>
</tr>
<tr>
<td>Ellis⁵</td>
<td>RCT</td>
<td>49</td>
<td>C</td>
<td>16 weeks</td>
<td>No association</td>
<td>Beneficial in subgroup</td>
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<tr>
<td>Cross⁶</td>
<td>L</td>
<td>69</td>
<td>C</td>
<td>~1 year</td>
<td>No association</td>
<td>Binary transformation only</td>
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<tr>
<td>Wilson⁷</td>
<td>C-S</td>
<td>118</td>
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<td>-</td>
<td>Detrimental on 2 tests</td>
<td>Binary transformation only Substance users only</td>
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<tr>
<td>Kahouadji⁸</td>
<td>C-S</td>
<td>93</td>
<td>B</td>
<td>-</td>
<td>Detrimental on 1 test</td>
<td>Methodological flaws</td>
</tr>
</tbody>
</table>

C-S = Cross-sectional, L = Longitudinal, RCT = Randomized clinical trial, C = Comprehensive, B = Brief, GSS = Genotype Susceptibility Score

Although CPE score seems to correlate with CSF viral efficacy, tailoring HAART regimens to prevent NCD over time is not yet indicated.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>NP</th>
<th>Duration</th>
<th>Finding</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciccarelli¹</td>
<td>101</td>
<td>C</td>
<td>-</td>
<td>Beneficial</td>
<td>2010 version stronger than 2008 version</td>
</tr>
<tr>
<td>Ciccarelli²</td>
<td>C-S</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Casado³</td>
<td>C-S</td>
<td></td>
<td></td>
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<tr>
<td>Vassallo⁴</td>
<td>L</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ellis⁵</td>
<td>RCT</td>
<td></td>
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<tr>
<td>Cross⁶</td>
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<td></td>
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<tr>
<td>Wilson⁷</td>
<td>C-S</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kahouadji⁸</td>
<td>C-S</td>
<td>93</td>
<td>B</td>
<td>Detrimental on 1 test</td>
<td>Methodological flaws</td>
</tr>
</tbody>
</table>

C-S = Cross-sectional, L = Longitudinal, RCT = Randomized clinical trial, C = Comprehensive, B = Brief, GSS = Genotype Susceptibility Score

HAND: Role of Antiretroviral therapy, independent of systemic infection.

- Positive impact of HAART could be dependent on CNS penetration/effect.

- Negative impact of HAART could be related to drug toxicity.
Efavirenz and NCD

- Short term CNS toxicities of EFV are well known.
- Long term administration may affect development of NCD.
Efavirenz and NCD

- 445 patients from the CHARTER cohort enrolled:
  - EFV 272 patients, median duration 17.9 m or LPV/rtv 173 patients, median duration 16.4 m
  - Baseline comprehensive NC testing included evaluation of seven cognitive abilities.
  - Raw scores were converted to $T$ scores, adjusted for demographics, then converted into deficit scores. Deficit scores were averaged to derive a global deficit score for each subject.

- Overall EFV users had worse performance in most NC abilities:
  - Verbal fluency and working memory were the most impaired.
  - Speed of information processing and executive functioning were also impaired.
  - An interaction with HCV status was associated with worse performance.

(Ma et al J. of Neurology 2015)
Discontinuation of HAART: effect on Neurocognitive function.

- AC TG 5107: observational data on patients who had stopped HAART.
- Subjects stopped HAART at the start of study and were followed for 96 weeks.
- All subjects who stopped therapy showed significant improvement in neurocognitive scores. Improvement continued off medication.
- Patients who restarted meds during the study did not show improvement.
- Both EFV containing and non EFV containing regimen discontinuation showed improvement.

  (Robertson et al. *Neurology* 2010)
Cognitive Performance During Treatment Interruption

- 167 subjects, mean CD4 > 400 before interruption; had been on cART > 4 years

Robertson et al, Neurology 2010
Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients
(Hoffman et al. HIV Medicine (2017), 18, 56—63)

- The estimated rates of AE’s and neuropsychiatric AE’s leading to discontinuation within 12 months of initiation of therapy were evaluated in 1704 patients (1950 regimens) prescribed an INSTI containing regimen.

- Discontinuation rates varied for the INSTI used:

<table>
<thead>
<tr>
<th>INSTI</th>
<th>Any AE%</th>
<th>NP AE %</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir</td>
<td>7.6</td>
<td>5.6</td>
<td>985</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>7.6</td>
<td>0.7</td>
<td>287</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>3.3</td>
<td>1.9</td>
<td>678</td>
</tr>
</tbody>
</table>

- NP AE’s were observed more frequently in women (HR 2.64), patients older than 60 (HR 2.86) and in HLA B5701- patients starting abacavir (HR2.42)
HAND: Role of Antiretroviral therapy.

- Positive impact of HAART could be dependent on CNS penetration/effect.
- Negative impact of HAART could be related to drug toxicity.

Despite data suggesting that some antiretroviral medications may have a detrimental effect on NC function, benefits of HAART seem to greatly outweigh any NC risks.
HAND: Biomarkers

- **Systemic:**
  - Plasma HIV RNA, HIV DNA in PBMC’s, sCD163

- **CSF:**
  - Neopterin, IL6, IL8, CCI2(MCP-1) IgG index have all been shown to be elevated in patients with HAND.
  - Neurofilament light protein is increased in untreated patients with NCD and decreases with treatment.
  - In some studies, tau protein has been elevated in the CSF in patients with HAND.
Elevated sCD163 Associated with Impairment

- 34 CHARTER (US) participants with suppressed plasma HIV RNA, on cART > 1 year; CD4 > 500

- CD163 = scavenger receptor involved in inflammation and secreted from monocytes as sCD163

Burdo et al AIDS 2013
Evidence of Ongoing Neuronal Injury Despite cART

- Neurofilament (NFL) is a major structural element of myelinated fibers
- NFL is elevated in cART vs. controls; 85 subjects on cART for > 1 year with plasma HIV RNA < 50 copies

Krut et al. PlosOne 2014
HAND: Biomarkers

- **Systemic:**
  - Plasma HIV RNA, HIV DNA in PBMC’s, sCD163

- **CSF:**
  - Neopterin, IL6, IL8, CCI2(MCP-1) IgG index have all been shown to be elevated in patients with HAND.
  - Neurofilament light protein is increased in untreated patients with HAND and decreases with treatment.
  - In some studies, tau protein has been elevated in the CSF in patients with HAND.

Although several plasma and CSF markers have been associated with HAND, no clear panel of markers has been identified.
HAND: Host Factors

- 575 (73% UDL) patients from Canadian cohort (NL 299 or ANI 276); NP testing base and 12m.: presence of ANI at baseline shorter time to progression, depression and smoking were associated with increased risk of progression. (Rourke CROI 2015 #465)

- Charter Cohort 191 controlled patients (80% either smoking or BMI>25), 15 NP tests q 6mo. For 3 years; 166 had CSF obtained. 23 patients declined (12%); only 10 had CSF HIV. Age, race, nadir CD4, CPE score, HCV, HTN, DM, AIDS and low hgb not associated. (Brouillette CROI 2015 #469)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &lt;50</td>
<td>6.80</td>
<td>1.35-34.23</td>
</tr>
<tr>
<td>HIV &gt;15 y</td>
<td>5.45</td>
<td>1.19-25.02</td>
</tr>
<tr>
<td>Education &lt;12y</td>
<td>4.25</td>
<td>1.45-12.42</td>
</tr>
<tr>
<td>CSF protein &gt;45g</td>
<td>3.25</td>
<td>1.13-9.35</td>
</tr>
</tbody>
</table>
VACS Index

- The Veterans Aging Cohort Study (VACS) Index was developed as a step towards creating an integrated endpoint for research and a potentially useful risk index for clinical management. One of the VACS Index hallmarks is that it combines age, along with traditional HIV biomarkers (i.e., HIV-1 plasma RNA and current CD4 count) and non-HIV biomarkers (i.e., indicators of renal [estimated glomerular filtration rate; eGFR] and liver [fibrosis index-4; FIB-4] function, anemia [hemoglobin], and Hepatitis C co-infection)\(^4-6\). By combining indicators of disease from multiple organs, it reflects the multisystem injury among people living with HIV disease.
VACS Index Correlated with Biomarkers of Inflammation

Justice AC et al, "Biomarkers of Inflammation, Coagulation, and Monocyte Activation are Strongly Associated with the VACS Index among Veterans on cART" CROI 2011 Poster # 796
HAND: Host Factors (VACS)

- 441 patients (407 treated, 71% UDL); battery of tests administered: 5 and 10 year cardiac risk scores (DAD5, Progetto Cuore10), VACS index, Screening NC tests (IHDS, Clock, Frontal assessment Battery), IHDS <10 received full NC testing. Poorer HAND scores were associated with higher cardiac scores and VACS index. (Calcagno CROI 2015 #487)

- 523 patients with UDL HIV, baseline and one follow up NP assessment. VACS index calculated. Higher VACS at baseline correlates with decline in overall NP function. Similar to CHARTER study in 2014. (Rourke CROI 2015 #467)
HAND: Host Factors

Mitochondrial DNA (mtDNA) haplogroups from 1027 patients in the CHARTER cohort were examined for association with NC results (GDS, HAND criteria). Multivariable models were adjusted for co-morbidities.

mtDNA haplogroup B was associated with less NCI (lower GDS and lower likelihood of GDS impairment {O.R. 0.16; P=.009} in persons of Hispanic ancestry but not African or European ancestry.

(Hulgan et al CID 2015)
HAND: Host Factors

Mitochondrial DNA (mtDNA) haplogroups from 1027 patients in the CHARTER cohort were examined for association with NC results (GDS, HAND criteria). Multivariable models were adjusted for co-morbidities.

mtDNA haplogroup B was associated with less NCI (lower GDS and lower likelihood of GDS impairment {O.R. 0.16; P = .009}) in persons of Hispanic ancestry but not African or European ancestry.

Host co-factors including co-morbidities, HIV/AIDS history, health behaviors and host genetic risks are involved to some degree in the development of HAND.

(Hulgan et al CID 2015)
HAND: Treatment

- 70 HIV + patients underwent NP testing, neuroimaging and physical activity survey: 22 active and 48 sedentary. Active patients performed significantly better on NP tests for executive function and putamen was significantly larger. (Basco CROI 2015 #488)

- 622 men in MACS cohort (44% HIV+) underwent IPAQ, METs and categorical physical activity survey (low, medium and high) as well as NP testing at baseline and q6 mo. follow up visits. HIV was not associated with any scores. Higher physical activity was associated with better psychomotor and executive functioning but did not change over time. (Monroe CROI 2015 # 489)
HAND treatment

- 14 suppressed HIV + patients with diagnosed HAND, Randomized to background HAART +/- maraviroc. NC testing for 5 domains at baseline, 6 and 12 months. Neuroimaging for metabolite concentration in BG and Frontal WM done at baseline and 12 months. Tropism data was not available on all patients.

- A trend was found in improved NC performance over time and intensified patients had stable markers of inflammatory metabolites which increased in control patients. (Gates CROI 2015 #441)

- Other agents being considered for treatment trials of HAND include minocycline, valproic acid, methotrexate, statins, fluconazole+SSRI and acectlylcholine esterase inhibitors
HAND treatment

- 14 suppressed HIV+ patients with diagnosed HAND, Randomized to background HAART +/- maraviroc. NC testing for 5 domains at baseline, 6 and 12 months. Neuroimaging for metabolite concentration in BG and Frontal WM done at baseline and 12 months. Tropism data was not available on all patients.

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- Other agents being considered for treatment trials of HAND include minocycline, valproic acid, methotrexate, statins, fluconazole+SSRI and acetylcholine esterase inhibitors.

- 17 well controlled patients received once daily dosing of cenicriviroc (CCR5 and CCR2 antagonist) for 24 weeks. Treatment was associated with improvements across several cognitive domains and in global neuropsychiatric performance. Improvements in plasma soluble CD14, CD163 and neopterin were also seen.

  (Nahlovu et al CROI 2107 Abstract # 381)
A5324

A Randomized, Double-Blinded, Placebo-Controlled Trial Comparing Antiretroviral Intensification with Maraviroc and Dolutegravir with No Intensification or Intensification with Dolutegravir Alone for the Treatment of Cognitive Impairment in HIV

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:
The National Institute of Allergy and Infectious Diseases
<table>
<thead>
<tr>
<th><strong>DURATION</strong></th>
<th>96 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAMPLE SIZE</strong></td>
<td>186 subjects</td>
</tr>
<tr>
<td><strong>POPULATION</strong></td>
<td>Subjects will have HIV-associated neurocognitive disorder (HAND) as defined by the Frascati criteria, plasma HIV-1 RNA &lt;50 copies/mL within 90 days prior to entry, and no more than one plasma HIV-1 RNA ≥50 and &lt;200 copies/mL in the past 6 months prior to entry with a subsequent plasma HIV-1 RNA &lt;50 copies/mL, and on stable ART for at least 12 months prior to entry with no plans to change treatment.</td>
</tr>
<tr>
<td><strong>STRATIFICATION</strong></td>
<td>Subjects will be randomized in a stratified manner. Stratification variables will be CD4+ nadir (≤100 vs. &gt;100 cells/mm³), and HAND severity (asymptomatic neurocognitive impairment [ANI] vs. mild neurocognitive disorder [MND] / HIV-associated dementia [HAD]).</td>
</tr>
<tr>
<td><strong>REGIMEN</strong></td>
<td>At entry subjects will be randomized to one of the following:</td>
</tr>
<tr>
<td>Arm A: Add to their existing ART: placebo for MVC and placebo for DTG</td>
<td></td>
</tr>
<tr>
<td>Arm B: Add to their existing ART: DTG and placebo for MVC</td>
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</tr>
<tr>
<td>Arm C: Add to their existing ART: MVC and DTG</td>
<td></td>
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### Schedule of Events

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<tr>
<th>Evaluation</th>
<th>2</th>
<th>4</th>
<th>12</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>96</th>
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<tbody>
<tr>
<td><strong>Visit Windows</strong></td>
<td>± 1 wk</td>
<td>± 2 wks</td>
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<td>Neurological Exam(^1)</td>
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<td><strong>Neurocognitive Batteries</strong></td>
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<td>HCV Ab</td>
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<td>Syphilis Screening</td>
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<td>Stored Serum(^2)</td>
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<td>CSF supernatant and pellets (only in subjects who undergo LP)</td>
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<td>PK Studies</td>
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</tr>
</tbody>
</table>

\(^1\) Only in subjects who undergo LP following CCR5 or CXCR4 genotyping.

\(^2\) Available through the Clinical Trials Office.

\(^3\) Available through the Clinical Trials Office.

\(^4\) Available through the Clinical Trials Office.
Take Home Points

- Clearly, treating HIV successfully is more likely to improve or preserve neurocognitive functioning in most patients. **Treatment interruptions are probably risky.**
- There are still no easy, reliable clinical or laboratory tools to help the busy clinician evaluate neurocognitive functions in patients.
- Some medications are more likely to cause CNS related adverse events.
- CNS targeted HAART may be appropriate in some patients and may be beneficial in symptomatic patients with demonstrated CSF viral escape.
Take Home Points

- Some co-morbidities may be more important cofactors in the development of NCD in HIV infected patients (HCV, CAD, Renal Disease).
- Host factors may be critically important in preserving neurocognitive function in HIV infected patients, much like HIV uninfected patients.
- There are no clear treatment options for virologically suppressed patients with NCD.
- New treatment options are being investigated.
Back to Lee

- Lee had several host factors that may have put him at increased risk for development of neurocognitive impairment: HBV infection, CAD, esophageal fistula, hyperlipidemia, age, years living with HIV.
- Viral escape may have played a role especially in light of his frequent treatment interruptions.
- His high level of executive functioning probably identified his neurocognitive decline earlier than most patients.
- Other than addressing co-morbidities and maintaining prolonged viral suppression, little additional treatment options exist that would have altered the course of Lee’s neurologic decline.
Questions?