Neuro-AIDS in drug users

NIDA conference  May, 2007

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HIV Neuroscience Program
NIMH Center for novel therapeutics
Johns Hopkins University
Neuro-AIDS in drug users

- Changes in HIV-D/MCMD/ANI definitions
- Changing phenotype of HIV-D with HAART
- Causes of comorbidity and fluctuations
- Impact of HAND on functional measures
- Surrogate biomarkers
- The treatment’ gap’ in HAND
- Design issues for treatment trials

Justin C McArthur JHU HIV
Neurosciences Program
Patients, volunteers, other investigators ~ NARC, NEAD

Clinical research/imaging:
K Carter, D Esposito, M Pomper, N Sacktor, A Venkataramana, R Skolasky, A King, G Mbeo, R Hurley, M Fitchett, M Greene, J Creighton, L Abrams

Neuropathology/Cutaneous Nerve studies: C Pardo, M Polydefkis, D Thomas, P Hauer, JW Griffin, B Freeman, B Dearman, G Ebenezer

Neuroimmunology and Models:
K Conant, S Gartner, N Haughey, A Hoke, A Nath

SIV macaque: J Clements, C Zink, J Mankowski, Laast V

JHU AIDS Service/CFAR:
J Bartlett, R Moore, J Gallant

$$ ~ NINDS, NIAID, NIMH, NARC, NIDA
• Osteopontin
• Mmp7 and snap25
• Peruzzi and synaptic changes.
The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale

Two methods to assess fluctuating confusion in dementia


CLINICAL IMPLICATIONS

- Brief standardised clinical scales are useful for identifying fluctuating confusion in patients with dementia.
- Standardised fluctuation scales may improve the accuracy of differential diagnosis between dementia with Lewy bodies and Alzheimer’s disease.
- An electroencephalogram examination also contributes important information to the assessment of fluctuating confusion.
• Fluctuating cognition with pronounced variations in attention and alertness is considered an essential diagnostic feature of DLB.
• FC has been observed in approximately 80% of DLB patients. In the original Consensus Guidelines for the clinical diagnosis of DLB, McKeith et al. described such fluctuations as deficits in cognitive function and global performance that alternate with periods of normal or near-normal performance. The periodicity and amplitude of fluctuations are variable both between subjects and within the same individual. They are described as occurring rapidly, although fluctuations can also be slower (weekly to months). No typical diurnal pattern of fluctuation has been identified in DLB. In the early stages, cognitive disturbances ranging from mild to severe, occurring within a period of a few weeks to a few days and sometimes even within hours, may alternate with periods of normal cognitive performance. A characteristic circadian pattern of presentation has not been described for DLB because the periodicity and range of fluctuation is quite variable within the same individual. In fact, apparent sudden spontaneous remissions are sometimes possible in response to new, unexpected situations in the patient’s life, although these are usually short-lasting.
New categorization of HAND

NIMH Frascati conference 2005: updated definitional criteria ~ addition of asymptomatic neurocognitive impairment
Assessment of definitional criteria

Cherner M., 2002

Improves diagnostic accuracy of AAN and HNRC nomenclatures with respect to post mortem presence of HIV encephalitis

**Positive Predictive Power:** Number of cases with NP impairment who eventually develop HIVE

<table>
<thead>
<tr>
<th></th>
<th>Using AAN criteria:</th>
<th>Using HNRC criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15/17 = 88%</td>
<td>18/19 = 95%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frascati</th>
<th>Normal</th>
<th>Asymptomatic</th>
<th>Neurocog. Imp.</th>
<th>MCMD</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical MSK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>1</td>
<td>19</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
HIV Infection/AIDS

HIV Associated Neurocognitive Disorders

HAND

Asymptomatic Neurocognitive Impairment

Mild neurocognitive Disorder

HAD

HIV Infection/AIDS
previous studies demonstrated that the psychostimulant methamphetamine (MA) and the human immunodeficiency virus-1 (HIV-1) protein Tat interacted to cause enhanced dopaminergic neurotoxicity. The present study examined whether tumor necrosis factor-alpha (TNF-α) mediates the interaction between Tat and MA. In Sprague–Dawley rats, injections of Tat caused a small but significant increase in striatal TNF-α level, whereas MA resulted in no change. The increase in TNF-α induced by Tat + MA was not significantly different from that induced by Tat alone. Temporal analysis of TNF-α levels revealed a 50-fold increase 4 h after Tat administration. In C57BL/6 mice, Tat + MA induced a 50% decline in striatal dopamine levels, which was significantly attenuated in mice lacking both receptors for TNF-α. TNF-α synthesis inhibitors significantly attenuated Tat + MA neurotoxicity in hippocampal neuronal culture. The results suggest that Tat-induced elevation of TNF-α may predispose the dopaminergic terminals to subsequent damage by MA.

$RCI = -1.47 + 0.32 \times CSF\ VL; \ R^2 = 0.06; \ p<.025.$

Linear Regression with 95% Mean Prediction Interval
Lessons from Alzheimer disease and Huntington disease

• Focus on MCI and presymptomatic HD, before transition to symptomatic disease
• Screening tests can identify MRI and PET abnormalities in MCI, or even presymptomatic stages
• Therapy now targeting early stages of AD and HD

FIGURE 1. Grey matter deficits spread through the limbic system in moderate AD.
<table>
<thead>
<tr>
<th>Subclassification of mild cognitive impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amnestic or single memory MCI</td>
</tr>
<tr>
<td>Multi-domains MCI (multiple domains slightly impaired)</td>
</tr>
<tr>
<td>Usually progresses to AD</td>
</tr>
<tr>
<td>Progresses to:</td>
</tr>
<tr>
<td>AD, vascular dementia, might represent normal ageing</td>
</tr>
<tr>
<td>Single non-memory MCI</td>
</tr>
<tr>
<td>Progresses to:</td>
</tr>
<tr>
<td>fronto-temporal dementia, Lewy body dementia, vascular dementia, primary progressive aphasia, Parkinson’s disease, AD</td>
</tr>
</tbody>
</table>

AD, Alzheimer’s disease; MCI, mild cognitive impairment.
Recognition that there is a spectrum of HIV-associated neurocognitive disturbances

- Asymptomatic neurocognitive impairment (ANI)
- Minor neurocognitive disorder
- HIV-associated dementia

In HAART recipients, approx. 40-60% have measurable neurocognitive deficits!
HIV and the AIDS Epidemic: 2007

- Global 2005: 64m living with HIV/AIDS, 11m deaths, and 5.3 million new infections
- HAART introduced 1996 ~ survival, but only reaching 5% of world’s HIV+. Global AIDS initiative: 3m by 2005 thru’ PEPFAR and other initiatives
- In 8 African countries, >20% adults are HIV+ decimating society
- In USA, HIV has become a chronic disease disproportionately affecting urban poor, African-Americans and Latinos.
- Concern that as OI’s come under control, so HAND may become common cause of neurological disability globally
HIV prevalence in adults in sub-Saharan Africa, 2001

- 20 – 39%
- 10 – 20%
- 5 – 10%
- 1 – 5%
- 0 – 1%
- Trend data unavailable
- Outside region
Incidence of HIV-associated Neurological Conditions
Johns Hopkins HIV Clinical Cohort
per 100 person years

HIV Dementia
HIV sensory neuropathy
Frequency of clinical features in JHU HIV-D cases (n=300)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td></td>
</tr>
<tr>
<td>Gait difficulty</td>
<td></td>
</tr>
<tr>
<td>Mental Slowing</td>
<td></td>
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<tr>
<td>Depressive Sx</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
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<tr>
<td>Behavioral change</td>
<td></td>
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<tr>
<td>Apathy</td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td></td>
</tr>
<tr>
<td>Motor Complaint</td>
<td></td>
</tr>
<tr>
<td>Mania</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td></td>
</tr>
</tbody>
</table>
HIV-dementia: severe psychomotor slowing
Changes in HIV dementia with HAART

- **5 months mean survival in 1993-1995 to 38.5 months in 1996-2000.** Dore, AIDS 2003

- **Before HAART:**

- **After HAART:**
  Mixed ‘cortical and subcortical’ features, with milder phenotype or MCMD. Frequent transitions and reversals. Synaptodendritic injury with much less CNS infection.
HIV-associated cognitive impairment is prevalent....

Prevalence and patterns of neurocognitive disorders pre- and post-HAART

- Prevalence of neurocognitive impairment was similar pre- and post-HAART (41% and 38%). Patterns were different with more effects post-HAART on learning efficiency and complex attention, and fewer effects on attention, verbal fluency, and visuo-constructional deficits. *Cysique LA J Neurovirol, 2004*

- Prevalence of HAND possibly even increased pre- and post-HAART. *Sacktor N, 2002*

<table>
<thead>
<tr>
<th>AAN Classification</th>
<th>1994 monoRx</th>
<th>1998 72% HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>25.0</td>
<td>30.4</td>
</tr>
<tr>
<td>MCMD</td>
<td>47.7</td>
<td>33.9</td>
</tr>
<tr>
<td>HIV-D</td>
<td>27.3</td>
<td>35.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.002</td>
</tr>
</tbody>
</table>

- Symptomatic HIV+: global mild cognitive impairment, with moderate impairment in attention, psychomotor speed, motor coordination and learning
- AIDS: global moderate cognitive impairment with
- HIV-D: most severe deficits in complex attention/psychomotor speed, and additional deficits in verbal fluency and verbal memory. Relative preservation of naming and visuospatial functions

Suggests that HIV-D deficits are a worse form of the milder impairment that is seen in AIDS and symptomatic HIV infection, but that there are also additional deficits...

- Symptomatic HIV+: global mild cognitive impairment, with moderate impairment in attention, psychomotor speed, motor coordination and learning
- AIDS: global moderate cognitive impairment with predominant deficits inattention, complex attention/psychomotor speed, learning, motor coordination, verbal memory and reasoning
- HIV-D: most severe deficits in complex attention/psychomotor speed, and additional deficits in verbal fluency and verbal memory. Relative preservation of naming and visuospatial function
- *Suggests that HIV-D deficits are a worse form of the milder impairment that is seen in AIDS and symptomatic HIV infection, but that there are also additional deficits*
HIV-associated cognitive impairment is dynamic.

<table>
<thead>
<tr>
<th>Transitions from NEAD I (1998) to NEAD II (2005)</th>
</tr>
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<tbody>
<tr>
<td>.</td>
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<tr>
<td>NEAD I Normal</td>
</tr>
<tr>
<td>NEAD I MCMD</td>
</tr>
<tr>
<td>NEAD I Mild</td>
</tr>
<tr>
<td>NEAD I Moderate</td>
</tr>
<tr>
<td>NEAD I Severe</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>State</th>
<th>NEAD2 Normal</th>
<th>NEAD2 MCMD</th>
<th>NEAD 2 Mild HAD</th>
<th>NEAD 2 Moderate</th>
<th>NEAD 2 Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>.</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>NEAD I Normal</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>NEAD I MCMD</td>
<td>8</td>
<td>24</td>
<td>13</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>NEAD I Mild</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>NEAD I Moderate</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>NEAD I Severe</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Persistence of Neuropsychologic Deficits Despite Long-Term Highly Active Antiretroviral Therapy in Patients With HIV-Related Neurocognitive Impairment

Prevalence and Risk Factors

Valerio Tozzi, MD,* Pietro Balestra, PsyD,* Rita Bellagamba, MD,* Angela Corpelongo, MD,* Maria Flora Salvatori, DSc,* Ubaldo Visco-Comandini, PhD,* Chrysoula Vlassi, MD,* Marinella Giulianelli, PsyD,* Simonetta Galgani, MD,† Andrea Antinori, MD,* and Pasquale Narciso, MD

TABLE 5. Factors Associated With Persistent NP Deficits in the 94 Impaired HIV-Positive Patients: Results of Multivariable Cox Model

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>1.18</td>
<td>0.23 to 5.88</td>
<td>0.844</td>
</tr>
<tr>
<td>Education (for 1-year decrease)</td>
<td>1.14</td>
<td>0.98 to 1.30</td>
<td>0.072</td>
</tr>
<tr>
<td>HCV-positive serology</td>
<td>0.96</td>
<td>0.34 to 2.76</td>
<td>0.937</td>
</tr>
<tr>
<td>CD4 count at last visit (for 1-cell increase)</td>
<td>1.00</td>
<td>0.99 to 1.00</td>
<td>0.205</td>
</tr>
<tr>
<td>NPZ8 baseline score (for 1° decrease)</td>
<td><strong>3.07</strong></td>
<td><strong>1.04 to 6.08</strong></td>
<td><strong>0.001</strong></td>
</tr>
</tbody>
</table>

**Conclusions:** The severity of NCI at HAART initiation seems to be the strongest predictor of persistent NP deficits despite long-term HAART. Our data indicate that HAART should be initiated as soon as NCI is diagnosed to avoid potentially irreversible neurologic damage.
• “Progressive” HAD (equivalent to “subacute” or “chronic active”)
• “Stable HAD” (fixed neurological deficits; previously called “chronic inactive”)
• “Improving HAD” (improving or regressing neurological deficits)
• “Fluctuating HAD” (fluctuating neurological deficits)
Other confounding illnesses in the assessment of HIV dementia

- Metabolic syndrome in HAART recipients and accelerated vascular disease (Currier, 2003)
- Immune restoration syndrome
- CNS escape
- Alcohol and other drugs of abuse
- Hepatitis C co-infection
- Age-related cognitive changes
- Vitamin, endocrine and nutritional deficiencies
- Resource-limited countries ~ TB

![Fig. 1. Cognitive functioning using the modified Memorial Sloan Kettering rating scale. MSK, Memorial Sloan Kettering. □ Young; □ old.](image-url)
The study reveals a dose × vocabulary score interaction, ie lower vocabulary appeared to have a greater impact from MDMA.
Effect of Tat+Methamphetamine treatment on striatal TH immunoreactivity

Theodore S. et al, 2006

Tat+MA (D, H) produced loss of TH reactivity in striatum

Effect of Tat+MA treatment on markers of oxidative stress in the striatum. Striatal synaptosomes were analyzed by a slot-blot method for the presence of protein carbonyls (a), 3-NT (b) and 4-HNE (c).
Ins in the hippocampus of adult rats during chronic ethanol treatment and correlations to behavioral impairments

Stijn Wirkner and Jörg Schramek

(w/v) ethanol over a period of 4, 12, and 36 weeks produced distinct alterations of the glial fibrillary acidic protein immunoreactivity (GFAP-IR) of dorsal hippocampal astrocytes. Down-regulation of the total GFAP-IR was measured in all examined brain regions after 36 weeks of ethanol treatment. Prolonged ethanol treatment in the cells. Regional differences in the vulnerability to the neurotoxic effects of chronic ethanol intake over 36 weeks were found: CA3 > CA1 + CA2 = CA4 > Gd. In agreement with the acquisition of maze performance using a complex elevated labyrinth was deteriorated after 36 weeks of ethanol treatment, suggesting a deficit in learning and structural and functional changes produced by chronic ethanol treatment.
Time course of fluctuations in different dementias

Dementia of Lewy body type ~ hours

HIV-dementia ~ weeks/months

Alzheimer ~ months/years
Causes of fluctuations in HIV dementia

- Substance abuse
- Depression and fatigue
- ART effects/adverse effects
- Immune reconstitution syndrome (IRIS)
- Non-IRIS cytokine effects
- CNS ‘escape’
- Mitochondrial effects/oxidative stress
- Astrocyte and symaptodendritic effects
CNS immune restoration syndrome

Subacute onset of a left hemiparesis; no fever or h/a; CSF JCV +

CD4 count: 9 rising to 157
pHIV: 4.7logs dropping to undetectable
CNS “escape”

- Acute neurological syndrome: usually encephalopathy with no CNS OI
  - Plasma HIV RNA levels << CSF
  - Differential includes CMV encephalitis, HSV encephalitis, IRS
  - Usual causes: non-CNS penetrant ART’s or poor adherence

Wendell K, McArthur JC, CID 2003
Case KE: reflecting poor CNS penetration?

- 47 man with 6 months history of progressive dementia, gait imbalance, and reduced verbal output.
- CD4 42, started Kaletra+Truvada 3 months before LP
- CSF: 2 wbc, protein 62,
  - CSF HIV 76k
  - plasma HIV 481

CNS escape
Mitochondria effects from ART exposure ~ CNS relevance

Log copy number of mtDNA per cell in subcutaneous limb fat by current NRTI exposure status. ART indicates antiretroviral therapy (from Cherry C, JAIDS 2006 42(4):435-40).

(A) A healthy Remak bundle at the papillary dermis containing 3 axons surrounded by collagen. (x25K); (B): HIV-associated sensory neuropathy. Remak bundle with dilated unmyelinated axons showing watery axoplasm and granular debris. From Ebenezer G. submitted Brain 2007.
Perivascular macrophages are the principal CNS targets of productive SIV and HIV infection:

Takahashi K, 1996; Williams K, 2001; Gartner S, 2001

Glass J
Pathogenesis of HIV-associated dementia

• Circulation and ingress of activated monocytes

• Productive CNS infection established, with reservoir in macrophages and astrocytes

• Release of inflammatory mediators and toxic HIV proteins (tat, gp120)

• Astrocytosis, BBB dysfunction and neuronal dysfunction, synaptic simplification
Mitochondria effects from ART exposure ~ ? CNS relevance

Log copy number of mtDNA per cell in subcutaneous limb fat by current NRTI exposure status. ART indicates antiretroviral therapy (from Cherry C, JAIDS 2006 42(4):435-40).

Abnormal mitochondria in dermal Remak bundle.
From Ebenezer G. submitted Brain 2007
Synaptodendritic injury in HIV dementia may be less permanent

Ellis, Langford, and Masliah.

Excess proteolysis of SYNAPTIC PROTEINS by MMP-7
Detection of integrated HIV-1 DNA in astrocytes and macrophages: ? permanent reservoirs of HIV

CD68 and p24 antigen in Macrophages and astrocytes

Laser capture microdissection from macrophage lineage cells

Laser capture microdissection from astrocytes

Churchill M., JNV, 2006
Neuropathologic Features of Cases Initially With an Isolated Amnestic Syndrome vs Those With Cognitive Impairment Involving Multiple Domains

<table>
<thead>
<tr>
<th>Neuropathologic Feature</th>
<th>Amnestic MCI Cases, No. (%)</th>
<th>Multiple-Domain MCI, No. (%)</th>
<th>P Value (Fisher Exact Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consensus pathologic diagnosis of AD</td>
<td>18 (75.0)</td>
<td>6 (60.0)</td>
<td>.43</td>
</tr>
<tr>
<td>Khachaturian criteria for AD</td>
<td>20 (83.0)</td>
<td>7 (70.0)</td>
<td>.39</td>
</tr>
<tr>
<td>CERAD criteria for AD*</td>
<td>15 (62.5)</td>
<td>3 (30.0)</td>
<td>.13</td>
</tr>
<tr>
<td>NIA-Reagan criteria for AD†</td>
<td>18 (75.0)</td>
<td>5 (50.0)</td>
<td>.23</td>
</tr>
<tr>
<td>Braak staging criteria for NFTs‡</td>
<td>20 (83.0)</td>
<td>8 (80.0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Vascular lesions present§</td>
<td>8 (33.3)</td>
<td>4 (40.0)</td>
<td>.71</td>
</tr>
<tr>
<td>AGD present</td>
<td>12 (50.0)</td>
<td>6 (60.0)</td>
<td>.72</td>
</tr>
<tr>
<td>Lewy bodies present</td>
<td>6 (25.0)</td>
<td>3 (30.0)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; AGD, argyrophilic grain disease; CERAD, Consortium to Establish a Registry for Alzheimer Disease; MCI, mild cognitive impairment; NFT, neurofibrillary tangle; NIA-Reagan, National Institutes of Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease.

*According to the CERAD scoring system, “no” refers to not AD or possible AD, and “yes” refers to probable or definite AD.
†According to the NIA-Reagan scoring system, no refers to not AD or low probability of AD and yes refers to moderate or high probability of AD.
‡According to Braak staging criteria, no refers to a Braak stage of I or II, and yes refers to a Braak stage of III, IV, V, or VI.
§Presence of vascular lesions determined to have contributed to the diagnosis of dementia.

Figure 2: Representative spectra for a patient with stable mild cognitive impairment (MCI-MCI), a patient with MCI who progressed to Alzheimer disease (MCI-AD), and a healthy control for ubiquitin (highlighted in low).
Comparison of Dana cohort (1994-7) and NEAD (1998-present): initially DANA on monotherapy (76%), but NEAD 72% on HAART

<table>
<thead>
<tr>
<th></th>
<th>Dana (n=272)</th>
<th>NEAD (n=376)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years mean (SD)</td>
<td>39.7 (7.5)</td>
<td>41.7 (7.2)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>77.9</td>
<td>70.5</td>
<td>0.03</td>
</tr>
<tr>
<td>(% White/Black/Hispanic/other)</td>
<td>50/40/7/3</td>
<td>23/65/10/2</td>
<td>0.001</td>
</tr>
<tr>
<td>Education : yrs, mean (SD)</td>
<td>13.5 (2.9)</td>
<td>12.5 (2.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>AIDS defining illness (%)</td>
<td>37.9</td>
<td>49.5</td>
<td>0.003</td>
</tr>
<tr>
<td>CD4+ count, mean (SD)*</td>
<td>177.9 (182.2)</td>
<td>136.0 (87.4)</td>
<td>0.30</td>
</tr>
<tr>
<td>AAN Classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>25.0</td>
<td>30.4</td>
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<td>47.7</td>
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<tr>
<td>HIV-D</td>
<td>27.3</td>
<td>35.8</td>
<td></td>
</tr>
</tbody>
</table>

* P value from t test comparing log-transformed CD4 counts
Prevalence of neurocognitive impairment was similar pre- and post-HAART (41% and 38%). Patterns were different with more effects on learning efficiency and complex attention, and relatively less on attention, verbal fluency, and visuoconstructional deficits. 

Cysique LA J Neurovirol, 2004
hip of antiretroviral treatment to postmortem brain tissue viral load in human immunodeficiency virus-infected patients.

Immunodeficiency virus (HIV)-1 invades the central nervous system (CNS) soon after infection and is partially protected there from host antiretroviral drugs (ARVs). Sanctuary from highly active antiretroviral therapy (HAART) in the CNS could result in ongoing viral replication, propment of drug resistance and neurological disease. Despite the importance of these risks, no previous study has directly assessed HAART brain tissue viral load (VL). The authors evaluated 61 HIV-infected individuals for whom both histories of HAART treatment and postmortem measurements were available. Two groups were defined based on HAART use in the 3 months prior to death: HAART(+) subjects had received HAART and HAART(-) subjects had not received HAART. HIV RNA was quantified in postmortem brain tissue (log10 copies/10 microg total tissue) and plasma (log10 copies/ml) by reverse transcriptase-polymerase chain reaction (RT-PCR). Brain tissue VLs were significantly lower among subjects compared to HAART(-) subjects (median 2.6 versus 4.1; P= .0007). These findings suggest that despite the limited CNS penetrative activity, HAART is at least partially effective in suppressing CNS viral replication. Because some HAART regimens may be better in this regard, regimen selection strategies could be used to impede CNS viral activity, limit neuronal dysfunction, and prevent or treat clinical disorders in HIV-infected patients. Furthermore, such strategies might help to prevent the development of ARV resistance.

798671 [PubMed - indexed for MEDLINE]
So what is everyday impact of HAND?
Impact of HIV dementia

- Survival: 3-fold higher risk of death
- Driving ability
- Work performance
- Medication adherence
- Less compliant with medical care?
- Less compliant with drug cessation?
- Less compliant with protective sex measures?
The impact of HIV-associated neuropsychological impairment on everyday functioning.


Heaton RK et al

To evaluate the functional, or "real-world" impact of HIV-associated NP impairment in 267 HIV-infected participants. All received comprehensive NP, neuromedical, and standardized functional evaluations that included laboratory measures of everyday functioning.

*Compared to NP-normal participants, those with NP impairment performed significantly worse on all laboratory measures of everyday functioning.*
Impact of HIV-D or MCMD on medication adherence

- *Hinkin C Neurology, 2002*

Neurocognitive compromise and complex medication regimens are associated with significantly lower adherence rates in OLDER subjects. Cognitively compromised participants on more complex regimens had the greatest difficulty with adherence.
Improving adherence to HAART in cognitively impaired HIV+ subjects: intervention study using a verbal prompting device  
Andrade A 2005

**Medication Adherence in Cognitively Impaired Subjects**

<table>
<thead>
<tr>
<th>Study Week</th>
<th>DMAS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>12</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>16</td>
<td>95</td>
<td>95</td>
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<tr>
<td>20</td>
<td>95</td>
<td>85</td>
</tr>
<tr>
<td>24</td>
<td>85</td>
<td>70</td>
</tr>
<tr>
<td>Overall</td>
<td>85</td>
<td>70</td>
</tr>
</tbody>
</table>

Legend: 
- **DMAS**
- **Control**
Change in HIV-1 Markers in intervention adherence study

* p<.05 relative to ARV education group
Surrogate markers in HIV-dementia

- ART Adherence
- MRS
- Functional MRI/PET
- Computerized motor testing
- CSF HIV RNA
- CSF immune activation markers
- CSF cellular injury markers
- Plasma immune activation markers
- Plasma proteomics
- Genetic markers of susceptibility or progression

Most of these have not been fully assessed or validated in the HAART era
Research biomarkers for HIV dementia or encephalitis (associative or predictive)

- CSF markers of oxidative stress: Haughey N, Ann Neurol, 2004
- Plasma proteomic markers: 4348 Da protein distinguishes HIV-D from non-demented (sensitivity 100%, specificity 75%) Luo X, Neurology. 2003 Jun 24;60:1931-7
- MCP1 promoter polymorphisms predict HAD Gonzales E. PNAS, 2002; Copy number of a segmental duplication for CCL3L1 (MIP-1alpha) affects disease susceptibility Gonzales E. Science. 2005
NEAD CSF HIV RNA compared to other studies

Mcarthur JC, Arch Neurol, 2004

\[
\text{Log}_{10} \text{ HIV RNA copies/ml CSF}
\]

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>MCMC</th>
<th>HIV-D Severe</th>
<th>MSK 2</th>
<th>MSK 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N=29</td>
<td>N=29</td>
<td>N=37</td>
<td>N=6</td>
<td>N=5</td>
</tr>
<tr>
<td>McArthur</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brew</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Historical Comparison
Pre-HAART
NEAD CSF HIV RNA compared to other studies

Mcarthur JC, Arch Neurol, 2004

Log₁₀ HIV RNA copies/ml

<table>
<thead>
<tr>
<th></th>
<th>NEAD Cohort</th>
<th>Historical Comparison Pre-HAART</th>
<th>HAART Era</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nml</td>
<td>McArthur</td>
<td>MSK 2 MSK 3</td>
<td></td>
</tr>
<tr>
<td>HIV+</td>
<td>HIV-D</td>
<td>N=6 N=5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=29 N=37 N=8</td>
<td>McArthur</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brew</td>
<td>Clifford</td>
<td>Mild Dementia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brew</td>
<td>Mild Brew</td>
</tr>
</tbody>
</table>

Comparison

NeuroAIDS Cohort Historical Comparison

Pre-HAART

HAART

NEAD Cohort

Historical Comparison

Pre-HAART

HAART Era
Biomarkers of oxidative stress can differentiate HAND phenotype: significant elevations of ceramide, and 4-HNE in ‘progressive’ HIV-dementia. *Haughey N, Ann Neurol, 2004*

- ND = not demented
- ID = stable dementia (MSK 1 or 2: no change)
- AD = progressive dementia (MSK 1 or 2: new transition)
Platelet and hemoglobin as markers of incident dementia
Wachtmann L  NEAD-2 study

Kaplan-Meier curves of the cumulative incidence of HIV-associated dementia by change from baseline platelet count and by hemoglobin levels in the North-East AIDS Dementia (NEAD) cohort.
The HIV+ adult cohort was stratified into four mutually exclusive genetic risk groups (GRGs) based on possession of a population-specific low or high number of *CCL3L1* copies (*CCL3L1*<sub>low</sub> or *CCL3L1*<sub>high</sub>) and disease-accelerating, i.e., detrimental (det) or nondetrimental (non-det) *CCR5* genotypes (*CCR5*<sub>det</sub> or *CCR5*<sub>non-det</sub>).

<table>
<thead>
<tr>
<th>AIDS-defining illness</th>
<th>n</th>
<th><em>CCL3L1</em>&lt;sub&gt;high&lt;/sub&gt;<em>CCR5</em>&lt;sub&gt;det&lt;/sub&gt;</th>
<th><em>CCL3L1</em>&lt;sub&gt;low&lt;/sub&gt;<em>CCR5</em>&lt;sub&gt;non-det&lt;/sub&gt;</th>
<th><em>CCL3L1</em>&lt;sub&gt;low&lt;/sub&gt;<em>CCR5</em>&lt;sub&gt;det&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RH</td>
<td>95% Cl</td>
<td>P</td>
<td>RH</td>
</tr>
<tr>
<td>CMV infection</td>
<td>100</td>
<td>1.53</td>
<td>0.71-3.30</td>
<td>0.278</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>33</td>
<td>3.27</td>
<td>0.98-10.87</td>
<td>0.053</td>
</tr>
<tr>
<td>Cryptosporidiosis</td>
<td>24</td>
<td>1.21</td>
<td>0.27-5.47</td>
<td>0.802</td>
</tr>
<tr>
<td>HAD</td>
<td>54</td>
<td>2.05</td>
<td>0.82-5.13</td>
<td>0.126</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>26</td>
<td>1.78</td>
<td>0.50-6.41</td>
<td>0.375</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>20</td>
<td>3.32</td>
<td>0.83-13.30</td>
<td>0.090</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>74</td>
<td>1.76</td>
<td>0.76-4.05</td>
<td>0.186</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>37</td>
<td>2.87</td>
<td>1.10-7.48</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Gonzales E… Ahuja S. et al Science, 2005
Research markers for HIV dementia or encephalitis

(associative or predictive)

HIV-D therapeutic strategies

- CNS penetration
- Compartmentalization of HIV genotypes
- HIV-dementia trials ~ HAART
- HIV-dementia trials ~ adjunctive therapies
- Questions for new trials
- Timing of initiation of HAART when HAND is detected?
Cartoon of pathological phases in HAND

Figure 3. CD4/CD16 dot plots of patient leukocytes. Staining performed using the whole blood lysis method. T-cells are CD4-bright, monocytes (middle panels) are CD4-dim.

<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>N</th>
<th>Percent CD16+ monocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mean</td>
</tr>
<tr>
<td>HIV+ MCMV/HIV-D</td>
<td>54</td>
<td>51.5</td>
</tr>
<tr>
<td>HIV+ neuro nmi</td>
<td>9</td>
<td>25.6</td>
</tr>
<tr>
<td>HIV- controls</td>
<td>6</td>
<td>11.5</td>
</tr>
</tbody>
</table>

Three-color immunophenotyping was performed using the whole blood lysis method and antibodies from BD Biosciences. Monocytes were defined as CD14+/CD4dim cells.
Cartoon of pathological phases in HAND

A. NO ANTIRETROVIRAL TREATMENT:
Activation of monocytes in marrow and blood results in enhanced monocyte ingress to CNS. This produces perivascular inflammation and foci of productive infection. End result: Neuronal/astrocytic death → progressive irreversible dementia

B. SUCCESSFUL ANTIRETROVIRAL TREATMENT:
With virological suppression there is reduced ingress of activated/infected monocytes. CNS inflammation is reduced and productive HIV infection in CNS is limited. Less injury of neurons and astrocytes and reversible dementia

1. Heightened activation of marrow monocytes entering circulation.
2. CNS entry of many HIV-infected or activated monocytes
3. Mφ activation and perivascular infection. Local release of inflammatory mediators
4. Astrocytic reaction and eventually death of astrocytes and neurons

Bone marrow

1. Controlled systemic replication; reduced egress of activated monocytes
2. Controlled peripheral and CNS infection; reduced entry of monocytes into CNS
3. Limited perivascular Macrophage activation; little release of inflammation mediators
4. Astrocyte and neuronal function remains normal or normalizes
HIV-dementia: severe psychomotor slowing improving *after* antiretroviral therapy.
MACS study: Trail Making Test, Part B (TM) performance partial correlation with virological response  

*Sacktor N, 2002*

This may be analogous with observation by S Deeks ~ CD4 response even in virological failures (NEJM 2001)
Choice of optimum HAART regimen for HIV dementia

Does CNS penetration profile matter?

- **Sacktor N, 2001**: no effect on cognitive function
- **Cysique L, 2004**: effect only in cognitively impaired
- **Letendre S., 2006**: new index of penetration
Psychomotor Speed improvements with HAART does NOT depend on HAART regimen.

Subjects on regimens containing *multiple* CNS-penetrating agents showed no significant differences on any tests of psychomotor speed, compared to those receiving regimens with only a *single* CNS-penetrating agent.

*Sacktor N, Neurology, 2001*
Suppression of HIV Replication in Plasma Requires Suppression of HIV Replication in CSF
C. Marra et al. ACTG 736

Conclusions
• CSF RNA was rarely detectable when plasma HIV RNA was <1000.
• Subjects with plasma HIV RNA >1000, were 5X more likely to achieve CSF suppression with an ART regimen with good CNS penetration.
• Achievement of an undetectable HIV RNA in both CSF and plasma was 3X more likely with an ART regimen with good CNS penetration.
• These results suggest that an antiretroviral regimen with good CNS penetration is important in achieving suppression of HIV RNA both in CSF and plasma.

Log Plasma HIV RNA
Log CSF HIV RNA
0 1 2 3 4 5
0 1 2 3 4 5 6 7 8

Log Plasma HIV RNA

## ART trials for HIV-dementia

<table>
<thead>
<tr>
<th>Agent</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>Positive effect on NP</td>
<td>High dose ZDV monotherapy. <em>Price RW, Ann Neurol 1993</em></td>
</tr>
<tr>
<td>Abacavir add on</td>
<td>No difference from background</td>
<td>Majority had RT resistance mutations. Run-in effect of background ART. <em>Brew BJ, under review</em></td>
</tr>
<tr>
<td>ZDV alternating ddi v. ZDV+ddI v. ZDV+ddC v. ZDV+ddI+NVP</td>
<td>Triple therapy or ZDV/ddI improved NP impairment</td>
<td>Not solely a trial of HIV-D; no protease inhibitors; all had CD4 &lt;50. <em>Price RW, AIDS 1999</em></td>
</tr>
<tr>
<td>HAART in Uganda</td>
<td>Positive effect on NP</td>
<td>First demonstration of reversal of HIV-D in RLC. <em>Sacktor N. 2006</em></td>
</tr>
</tbody>
</table>
Abacavir 3001 HIV-D trial: abacavir or placebo added to stable HAART (n=105)

Brew BJ PLOS, 2007

Improved NP Z score  Drop in CSF HIV RNA

Better

NP all

CSF HIV

Better
Conclusions:

Four factors compromised the study:

• pre-existing ABC resistance
• the unexpected continuing, prolonged and beneficial effect of HAART upon HAND
• The variability of the NP data was much greater than expected reducing the likelihood of detecting treatment differences
• HAD may have been 'burnt out', eg immune activation markes were normal in >80%
### Placebo Controlled Trials of Adjunctive Agents for HIV Dementia

<table>
<thead>
<tr>
<th>Agent</th>
<th>Action</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nimodipine</td>
<td>Calcium channel</td>
<td>NP trend</td>
</tr>
<tr>
<td>Selegilene</td>
<td>Anti-oxidant</td>
<td>+ NP effect</td>
</tr>
<tr>
<td>OPC14117</td>
<td>Anti-oxidant</td>
<td>NP trend</td>
</tr>
<tr>
<td>Thiocytic acid v selegilene</td>
<td>Anti-oxidants</td>
<td>+ NP effect for selegilene.</td>
</tr>
<tr>
<td>Lexipafant</td>
<td>PAF antagonist</td>
<td>+ NP effect</td>
</tr>
<tr>
<td>Memantine</td>
<td>NMDA antagonist</td>
<td>+ delayed NP effect</td>
</tr>
<tr>
<td>CPI-1189</td>
<td>?TNF antagonist</td>
<td>No effect</td>
</tr>
<tr>
<td>Peptide T</td>
<td>? Chemokine antag</td>
<td>No effect</td>
</tr>
</tbody>
</table>
So why have these trials not had more effect on clinical practice?

- Modest effect
- Questionable functional impact
- Slow accrual
- Slow reporting with average delay of 2-3 years!
- Poor PR
- Limited community and Pharma ‘buy in’ for trials
- Not always the right question at the right time ~ eg augmentation with abacavir as one drug in resistant subjects
Addressing the therapeutic ‘gap’

Osteopontin prevents monocyte recirculation and apoptosis

Tricia H. Burdo,* Malcolm R. Wood,† and Howard S. Fox*†

*Molecular and Integrative Neurosciences Department and †Core Microscopy Facility, The Scripps Research Institute, La Jolla, California, USA
Potential novel therapies for HAND?

- GF120918 (*MDR* modulator)
- maxi-HAART regimens
- Integrase inhibitors
- chemokine receptor blockers
- EPO
- MCP-1 blockers
- SSRIs
- Valproic acid
- neuroimmunophilin ligands
- cyclin-dependent kinase (cdk) inhibitors
- minocycline
Minocycline

• Second generation tetracycline with good CNS penetration and proven safety
• Effective in vitro at low viral doses even against R5 and X4R5 viruses, and in single-cycle reporter cell assays.
• C Zink demonstrated significant effect on SIVE JAMA, 2005
• N Sacktor has now initiated an ACTG trial in USA, and proposed one in Uganda
Fluoxetine protects rat hippocampal cultures vs. 3-NP and Tat toxicities
Utility of measurement of CSF HIV RNA in HIV-D

- Not diagnostic of HIV dementia
- In established HIV dementia: to assay CSF genotype and then follow CSF HIV RNA to assess CNS efficacy of a new regimen
- Identification of occasional cases of “CNS escape” ~ where CNS replication >> systemic replication
Drug Discovery Research Timeline

**Exploratory Discovery Research**
(Compound Screening, D-R, molecular modeling and Chemical synthesis)

**Lead Optimization**
Pharmaceutics Profiling, Toxicity, In vivo Proof-of-Concept

**Clinical Candidate Identified**
(Pharmacology, GLP Tox, DMPK, Safety, Compound Manufacturing)

**IND filed**

**Clinical Trials**
Ph I Safety & PK  
Ph II Dose Range-Finding, P-O-C  
Ph III Confirmatory

**NDA**

---

Agent class #1

Agent class #2
Post HAART patients were grouped based on changing cognitive status

**Associative**
- HIV-not demented (HIV-ND)
- HIV-inactive dementia (HIV-ID)
- HIV-active dementia (HIV-AD) (worse)

**Predictive**
- HIV-not demented (HIV-ND)
- MSK-stable (MSK-stb)
- MSK-improved (MSK-imp)
- MSK-worse (MSK-wor)
MRS correlates in HIV-dementia

• ↓ NAA, ↑ CHO, ↑ MI on SV-MRS (Barker P; Chang L; Navia B)
• SV-MRS abnormalities in mild neurological dz (Gonzales G; Chang L).
• Correlates with NP testing, CSF HIV RNA levels (Chang L); and immune activation markers (Ryan, Gendelman)
• Normalizes with HAART, but changes can take 9 months (Chang L)
• Not confirmed in other HIV+ groups
Novel measures for HIV-D ?: dopamine PET in HIV-D *Chang Brain 2004*
Figure 5. (A) In order to activate the visual cortex and lenticular nuclei, participants were to press keys on a keypad that corresponded to numbers presented in the center of a flickering checkerboard stimulus. Cerebral blood flow, determined via arterial spin labeling, is shown for (B) lenticular nuclei and (C) visual cortex of acute and early infection cases.
Is there a therapeutic ‘gap’ for HAND?

- Despite HAART’s effect on incidence, prevalence of HAND remains high.
- Neuronal loss is presumably permanent, even when CNS inflammation is ‘burnt out’.
- HAART can reverse neurocognitive deficits, but usually is only partial.

![Graph showing Z score change (Mean) with SDMT, TMB, and GP nondom for Single CSF penetrating agent and Multiple CSF penetrating agent.](chart.png)

Sacktor 2001
Design of ART and adjunctive trials for HIV-D ~ clinically relevant questions

- How reversible is HAND, and when should treatment start?
- If virological suppression is complete, will this protect against HAND?
- What is needed to close treatment gap?
- What are the determinants of treatment response?
- How can we dissect comorbidities?
- Can we improve outcome measures to reduce variability and sample size?
Challenges for the NeuroAIDS community

- Identify neurological priorities for NIH, national AIDS organizations, and support NARC
- Emphasize prevalence and functional importance of HIV-D, MCMD, and ANI
- Develop clinically useful predictive and surrogate markers
- Design and conduct controlled clinical trials rapidly and with large enough numbers to impact practice
- Recognize limitations of current definitional criteria and of autopsy-based series
- Develop therapies and outcome measures that can be applied in resource-limited settings
To date, no therapies, diagnostics, or predictive markers have entered clinical practice.