Overview

- HIV associated neurocognitive disorder (HAND) in 2016 - issues relevant to treatment, e.g., impact of cerebrovascular disease and neurodegenerative disease
- Antiretroviral treatment of HAND
- Adjunctive therapies for HAND
- Non-pharmacological treatments for HAND
HAND in 2016: Why is HIV-associated cognitive impairment still important?

• People living with HIV: 36.7 million

• 25 million (71%) live in Sub-Saharan Africa (15% > age 50)

• 16-41% of HIV+ individuals presenting to an ID clinic in Uganda diagnosed with dementia (Wang et al, 2007; Sacktor et al, 2013)

• 46% of adults living with HIV accessing ART

• HIV is the likely 3rd most common cause of dementia in the world, but unlike Alzheimer’s disease and vascular is treatable and reversible with early diagnosis
The Aging of the HIV Population

• As of 2015, more than one-half of all HIV-infected individuals in the US are aged > 50 years.

From France, D. New York Magazine, 11/1/09

Adopted from Luther et al., 2007
Higher Frequency of HIV Dementia among older (> age 50) vs. younger (age 20-39) HIV+ individuals (Hawaii Aging with HIV Study)

Valcour et al, Neurology, 2004
Persistent abnormality in CNS despite viral suppression on ART


- Neuroimaging markers: (caudate/putamen and cortical atrophy), Becker et al, for the MACS study, Brain Imaging and Behavior, 2011
Cerebrovascular Disease as a Potential Cause of Cognitive Impairment Among Older HIV+ Individuals
Aging amplifies HIV neurocognitive impairment: the effects may be related to vascular and metabolic factors
Heaton et al, ISNV 2012, J Neurovirol 18 (Suppl 1) S46

• 1521 HIV+ individuals from CHARTER study examined
• Significant age interactions with systolic blood pressure, body mass index (BMI), cholesterol, and AIDS diagnosis in predicting worse neuropsychological testing performance [global deficit score (GDS)]
• Conclusion: As HIV+ individuals age, there is a disproportionate reduction in neurocognitive performance, and both severity of HIV disease and indicators of vascular diseases of aging may contribute to these effects
Treatment of vascular risk factors impacts cognition in HAND (Foley et al, Clin Neuropsychol 2010)

- Cerebrovascular risk factors are associated with slower processing speed in HIV+ individuals (Mean age 44 years)
- HIV+ individuals with pharmacologically untreated vascular risk factors had reduced processing speed and executive functioning relative to those on medication
Potential Future Therapies for Cerebrovascular disease and HAND

- Pitavastatin

- Tesamorelin (Rx abdominal obesity by normalizing growth hormone and increases insulin like neurotrophic growth factor) (Ellis R)
Abnormal amyloid accumulation in HIV infection: Could Alzheimer’s disease be a potential cause of cognitive impairment in older HIV+ individuals?
Brain deposition of beta-amyloid is a common feature in HIV+ patients (age 31-58 years) (Green et al AIDS 2005)

- Amyloid is increased in diffuse non-neuritic plaques in HIV+ brains
- An increase in diffuse plaques suggest early aging with HIV infection and may be enough to cause cognitive impairment
Increased posterior amyloid uptake in a 64 year old HIV+ patient with ANI
Conceps of HAND pathogenesis: 2016

- Blood-Brain Barrier
- Blood
- CNS
- Macrophage activation & infection
- Chemokines
- Cytokines
- Glutamate
- Bioenergetic disturbance
- Neurotoxic viral proteins
- Uninfected and HIV Infected Monocytes
- Systemic inflammation, microbial translocation products
- Astrocyte activation & restricted infection
- Microglial activation/infection
- Lymphocyte infiltration
- Neurons
- Synaptodendritic pruning, neuronal injury
Cerebrospinal fluid metabolomics implicate bioenergetic adaptation as a neural mechanism regulating shifts in cognitive states in HIV-infected patients  

Dickens et al, 2015. AIDS

- Cognitive worsening: Excessive aerobic glycolysis
- Citrate accumulates when the glycolytic rate exceeds the capacity of the Krebs cycle
- Cognitive improvement: shift to anaerobic glycolysis

Adapted from: Ramsköld et al. Wikipathways
Antiretroviral Treatment of HIV-associated Neurocognitive Disorders
## CNS Penetration-Effectiveness Ranks 2016

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<td>Tipranavir-r</td>
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<td><strong>Fusion / Entry Inhibitors</strong></td>
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<td>Maraviroc</td>
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<td>Enfuvirtide</td>
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<td>Dolutegravir</td>
<td>Raltegravir</td>
<td>Elvitegravir</td>
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</table>
Better CNS penetration of ART is associated with better CSF virological suppression

Canadian Cohort: No Correlation of CPE Score and NP Function on ART

- 834 HIV+ patients from Ontario HIV Treatment Network Cohort Study\(^1\)
  - Regimen CNS penetration scored using CPE 2010; neuropsychological (NP) impairment assessed by Global NP Impairment Rating and Global NP Deficit Score

\[ P = .41 \]

Rourke SB, et al. IAS 2011. Abstract MOAB0104. Modified from Joel Gallant MD
CIT2 Study: a randomized study to compare CNS penetrating vs non CNS penetrating HAART

<table>
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<tr>
<th></th>
<th>CNS-T (n=26)</th>
<th>Non-CNS ART (n=23)</th>
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<th>P value</th>
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<tr>
<td>Adjusted Global deficit scale</td>
<td>-0.14 (0.54)</td>
<td>-0.07 (0.43)</td>
<td>0.09 (-0.48, 0.65)</td>
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<td>(Mean SD)</td>
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<tr>
<td>Plasma VL &lt; 50 Week 16 %</td>
<td>54%</td>
<td>82%</td>
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<td>0.065</td>
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<td>CSF VL&lt;50 Week 16 %</td>
<td>68%</td>
<td>87%</td>
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<td>0.17</td>
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<tr>
<td>CD4 Change Week 16 Mean (SD)</td>
<td>+41 (104)</td>
<td>+55 (154)</td>
<td>--</td>
<td>0.33</td>
</tr>
</tbody>
</table>

• No benefit from using CNS penetrating HAART compared to non CNS penetrating HAART on improving cognitive performance
Potential Neurotoxicity of Antiretroviral Drugs

• Robertson et al, Neurology 2010:1260-1266. In 167 HIV+ patients with CD4 >350 with ART treatment stopped, NP improved after cessation of ART

• Canilglia et al Neurology 2014:134-141. HIV-CAUSAL collaboration of 51,938 HIV+ ARV-naïve individuals initiating ART. High (>9) CPE regimens had increased risk of HIV dementia (Hazard ratio=1.74) vs those on low (<8) CPE regimen
ACTG 5303: A Double Blind Randomized Placebo Controlled trial of Maraviroc vs Tenofovir: Effect on Neurocognition
Robertson et al, 2016 AIDS 30:2315-2321

• 48 week trial among 262 ART naïve, CCR5 tropic HIV+ individuals who received either maraviroc 150 mg or tenofovir 300mg on a background of ritonavir-boosted darunavir and emtricitabine

• 49% of participants with cognitive impairment at baseline improved to normal cognition

• No differences in NP between maraviroc and tenofovir

• Similar efficacy in suppressing plasma viremia for both groups

• Conclusion: ART initiation with either maraviroc or tenofovir containing regimens improved neurocognitive function
Maraviroc Intensification

• Gates et al, AIDS 2016, 591-600. Maraviroc-intensified combined antiretroviral therapy improves cognition in virally suppressed HAND

• Tiraboschi et al HIV Med 2015, 388-392. Trend for improvement in cognition after switching to maraviroc in patients with HAND

• Conclusion: Maraviroc may have a benefit when used to intensify ART, rather than comparing it to standard tenofovir-based regimen in ART naïve patients
New antiretroviral drug trials now open for treating HAND

• ACTG 5324- Neurointensification study of dolutegravir and maraviroc in addition to cART
  • Phase 4 randomized, double-blind, placebo-controlled study of neurocognition in 186 patients with HAND for 96 weeks
  • Patients to receive either
    1) current ART and placebo,
    2) current ART and dolutegravir,
    3) current ART and dolutegravir and maraviroc
Adjunctive Therapies for the Treatment of HAND
# Placebo controlled trials of adjunctive agents for HIV dementia

<table>
<thead>
<tr>
<th>Agent</th>
<th>Action</th>
<th>Conclusions</th>
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<tr>
<td>Nimodipine</td>
<td>Calcium channel</td>
<td>NP trend</td>
</tr>
<tr>
<td>Peptide T</td>
<td>CCR5 inhibitor</td>
<td>No effect</td>
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<tr>
<td>OPC14117</td>
<td>Anti-oxidant</td>
<td>NP trend</td>
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<td>Thiocytic acid</td>
<td>Anti-oxidant</td>
<td>Selegiline NP effect</td>
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<td>v selegiline</td>
<td>Neuroprotectant</td>
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<td>STS</td>
<td>Neuroprotectant</td>
<td>NP effect</td>
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<td>PAF antagonist</td>
<td>NP effect</td>
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<td>NMDA antagonist</td>
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<td>CPI-1189</td>
<td>? TNF antagonist</td>
<td>NP trend</td>
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<td>STS (ACTG5090)</td>
<td>Neuroprotectant</td>
<td>No effect</td>
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<tr>
<td>Minocycline</td>
<td>Neuroprotectant</td>
<td>No effect on NP, lipid oxidative stress marker benefit</td>
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</tbody>
</table>
High Throughput Screening of Potential Compounds to Treat HAND (Joe Steiner)

- 2000 FDA approved compounds for human use were screened for neuroprotective effects in an *in vitro* model of oxidative stress-mediated cytotoxicity against HIV proteins.
- Rat mixed hippocampal cultures were pre-incubated with various concentrations of compounds for 1 hour prior to exposure to a wide variety of neurotoxins including HIV Tat protein.
- Both paroxetine and fluconazole protected hippocampal neurons as measured by cell survival quantified with a mitochondrial membrane potential assay.

![Graph](image)
Paroxetine and Fluconazole (Paraflu)
Study: Specific Aims

• To evaluate the safety and tolerability of paroxetine and fluconazole in HIV+ individuals with HAND.

• To evaluate the effect of paroxetine and/or fluconazole on neurocognitive performance, CSF lipid and protein markers of oxidative stress, CSF markers of macrophage/monocyte activation, inflammation, and neuronal injury, functional performance and neuroimaging markers in HIV+ individuals with HAND.
Paraflu Study Design

• 24 week, double-blind, placebo-controlled 2 x 2 factorial design Phase I/II study in 45 HIV+ individuals with HAND

• Participants were randomly assigned to 1 of 4 groups:
  1) Paroxetine 20mg orally every evening per day
  2) Fluconazole 100mg orally every 12 hours per day
  3) Paroxetine 20mg every evening and fluconazole 100mg every 12 hours orally per day
  4) Matching Placebo
Study Completion

- 45 HIV+ individuals were enrolled and analyzed in intent-to-treat analyses

- Treatment assignment
  - 11 received placebo
  - 11 received paroxetine
  - 11 received fluconazole
  - 12 received paroxetine and fluconazole

- 24 HIV+ individuals were included in as-treated analyses (>90% adherence)
Safety Results

• There were no differences in the frequency of adverse events (AE’s), (total or moderate/severe AE’s) or safety labs between the 4 treatment groups.

AE’s seen in > 1 subject

Placebo (n=11): diarrhea-2
Paroxetine only (n=11): sexual dysfunction-3, headache-2, insomnia-2, disturbing dreams-2
Fluconazole only (n=11): nausea-4, depressed mood-2, dry mouth-2,
Paroxetine and Fluconazole (n=12): diarrhea-5, nausea-4, dizziness-2, dry mouth-2
HIV+ individuals receiving paroxetine (alone or in combination with fluconazole) showed a benefit on the NPZ8 summary measure of NP performance (0.16 vs -0.32, p=0.032), the CalCAP sequential reaction time, (CalCAP Z score mean change = 0.44 vs -0.20, p=0.023), a test of executive function, but worse performance on the Trail Making Part A test (0.0 vs 0.38, p=0.006) compared to the no paroxetine arms (placebo or fluconazole alone), after adjusting for baseline NP test score, depression symptomatology.

There was no benefit for other individual tests or in depression symptomatology as measured by the CES-D score for paroxetine arms vs. no paroxetine arms.

HIV+ individuals receiving fluconazole showed no benefit compared to the no fluconazole arms.
Serum and CSF Immune and Neuronal Injury Markers

- HIV+ individuals receiving paroxetine (alone or in combination with fluconazole) had decreased serum CD163 (Mean change = -44.3 ng/mL) compared to the no paroxetine arms (placebo and fluconazole alone, Mean change = 358.0 ng/mL) (p= 0.003), after adjusting for baseline level suggesting less systemic macrophage activation in as treated analyses.

- There were no differences in HIV+ individuals receiving fluconazole vs no fluconazole in these immune and neuronal injury markers in as treated analyses.

- With intent to treat analyses, HIV+ individuals receiving fluconazole (alone or in combination with paroxetine) had decreased serum CD163 (Mean change = -138.1 vs -26.7, p= 0.014) and decreased serum neopterin (Mean change = 0.05 vs 0.48, p=0.043) compared to the no fluconazole arms (placebo and paroxetine alone) after adjusting for baseline level, suggesting decreased systemic macrophage activation and inflammation.
Paroxetine/Fluconazole Study: Summary

- Paroxetine and fluconazole treatment were safe and well tolerated in HIV+ individuals with HAND.
- Paroxetine treatment may be associated with cognitive improvement in several tests, even after adjusting for depression symptomatology, but worse performance in 1 other test.
- Paroxetine may also be associated with less systemic macrophage activation.
- Fluconazole treatment may be associated with a decrease in inflammatory and immunological markers, but this did not translate to neurocognitive benefit.
New Adjunctive Therapy Trials for HAND Now Open

• Anakinra, IL-1 receptor antagonist, PI Avi Nath, (NIH, Johns Hopkins)

  • Open label, phase 1 dose escalation study (100mg/day SC up to 300 mg/day) over 8 weeks in 12 patients with HAND
Insulin and HAND

- Insulin signaling contributes to synaptic remodeling and modulates glucose utilization in hippocampus facilitating memory.
- Insulin dysregulation is associated with chronic immune activation (Creely, 2007).
- In HAND insulin may have neuroprotective effect via shift from aerobic glycolysis to anaerobic glycolysis.
- Intranasal delivery of insulin via bulk flow along olfactory and trigeminal perivascular channels, and slower delivery via olfactory bulb axonal transport may enhance cognition in normal individuals, and people with AD and DM (Craft S.)
Inflammatory, excitotoxic, and HIV-protein associated neuronal death is attenuated by insulin in primary hippocampal neurons

*Haughey N.*, 2014

R5-gp120 induced dendritic damage is rescued by insulin
Intranasal insulin corrects behavioral deficits in EcoHIV infected mice

Potash et al., 2005. PNAS

Slusher and Volsky unpublished
<table>
<thead>
<tr>
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<th>Dose of Intranasal Insulin Tested</th>
<th>Patient Population</th>
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<td>2. Voice onset time (immediate/delayed recall ratio)</td>
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<td>3. Cerebral glutamate concentration</td>
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New adjunctive therapy trial for HAND opening early 2017

• Intranasal administration of insulin

• 40 patient study, 2017-2019
**Aim 1: To examine whether IMT is safe and well tolerated in individuals with HAND**

- Primary outcome measures:
  1) Adverse event frequency.
  2) Cognitive performance
  3) Functional performance
  4) Pharmacokinetics of intranasal insulin in blood and CSF

**Aim 2: To examine whether intranasal insulin improves neuroimaging markers of CNS injury.**

- Primary outcome measures:
  1) Single voxel-magnetic resonance spectroscopy (SV-MRS) myoinositol, choline, and N-acetyl aspartate concentrations in frontal white matter and basal ganglia.

- Secondary outcome measures:
  1) Diffusion tensor imaging (DTI) whole brain fractional anisotropy, DTI whole brain mean diffusivity
  2) Arterial spin labeling (ASL)

**Aim 3: To examine whether intranasal insulin improves CSF surrogate markers of oxidative stress, axonal injury, inflammation and abnormal amyloid metabolism.**

- Primary outcome measures:
  1) Surrogate measures of cell stress, neuronal injury/protection, oxidative stress, energy metabolism, amyloid cascade, immune activation and insulin sensitivity.

- Secondary outcome measures:
  1) Amyloid cascade, immune activation and insulin
Potential Future Adjunctive Therapies for HAND

- Novel antioxidants, eg, inhibitors of cystine/glutamate transporter (xc−) (Slusher B)
- Neutral sphingomyelinase inhibitors
- Glutaminase inhibitors
- Immunomodulators, eg dimethyl fumarate (Kolson D)
Potential Future Symptomatic Therapies for HAND

- Dopamine agonist- ropinirole with SSRI escitalopram (Goodkin K)

- Attention-enhancers, eg, modafanil
Non-Pharmacological Treatment of HAND; Role of Sleep Hygiene

• Gamaldo et al, JAIDS 2013: 609-616. 37% of HIV+ patients with chronic partial sleep deprivation (measured by polysomnogram, 2 week actigraphy), and validated sleep questionnaires which was associated with worse performance on tests of psychomotor speed and executive function.

• Pilot study of cognitive behavioral therapy and novel sleep app to improve sleep hygiene among patients with HAND underway (Gamaldo- Johns Hopkins)
Treatment of HAND-2016

• CART with complete HIV RNA suppression
• Rx associated symptoms- e.g., depression, insomnia
• Rx risk factors- e.g., cerebrovascular- ASA, statins, diabetes Rx, hepatitis C Rx
• Rx Etoh, illicit drug use- detox programs
• Increase physical activity, ? improved sleep hygiene
• Clinical trials of adjunctive agents- anakinra, intranasal insulin, ? paroxetine
Collaborators

**Johns Hopkins**
- Richard Skolasky
- Jason Creighton
- Richard Moxley
- Heidi Roosa
- Vince Rogalski
- Norman Haughey
- Peter Barker
- Mona Mohamed
- Justin McArthur
- Barbara Slusher

**Mayo Clinic**
- Michelle Mielke

**NINDS**
- Carol Anderson
- Avi Nath
- Joseph Steiner