The Mind Matters: Current Evidence on HIV, and the Brain

Igor Grant, MD, FRCP(C)
Director
HIV Neurobehavioral Research Program
University of California, San Diego

HIV DISEASE

- Neuromedical
- Neurobehavioral
HIV Neurobehavioral Disturbances

HIV Associated Neurocognitive disorders (HAND)

Primary HAND
- Asymptomatic neurocognitive impairment
- Mild neurocognitive disorder
- HIV-associated dementia

Secondary HAND
- Infection
- Neoplasia
- Cerebrovascular
- Nutritional
- Treatment related

Emotional & other behavioral

New Onset
- Depression
- Anxiety
- Adjustment disorders
- HIV mania
- HIV psychosis

Pre-exist / recurrent / comorbid
- Mood disorders
- Substance use disorders
- Other mental disorders

Combination antivirals prolong survival but NeuroAIDS remains prevalent

Heaton RK, et al. (2010). Neurology, 75, 2087-2096
HAND in Pre-CART and CART Eras by AIDS Status


Asymptomatic Neuropsychological Impairment
- abnormality in two or more cognitive abilities

Mild Neurocognitive Disorder
- cognitive impairment with mild functional impairment

HIV-associated Dementia
- marked cognitive impairment with marked functional impairment

HIV Associated Neurocognitive Disorders (HAND): Frascati Criteria

Antinori, et al., Neurology 2007
Prevalence of HAND by stage of HIV disease

NP = neuropsychologically impaired; MND = mild neurocognitive disease

NC Impairment by Domain in HIV+ Samples from Pre-CART and Post-CART Eras (NCI only)

* p<.05; ** p<.01; ***p<.001

**Neuropsychological course for HIV neurocognitive states**

- stably normal n=249
- stably impaired n=60
- stably improved n=95
- stably declined n=24
- Fluctuated n=102

![Graph showing the distribution of different neurocognitive states among HIV+ individuals.](image)

**HIV neurobehavioral disturbances**

- **HIV Associated Neurocognitive disorders (HAND)**
  - **Primary HAND**
    - Asymptomatic neurocognitive impairment
    - Mild neurocognitive disorder
    - HIV-associated dementia
  - **Secondary HAND**
    - Infection
    - Neoplasia
    - Cerebrovascular
    - Nutritional
    - Treatment related

- **Emotional & other behavioral**
  - New Onset
    - Depression
    - Anxiety
    - Adjustment disorders
    - HIV mania
    - HIV psychosis
  - Pre-exist / recurrent / comorbid
    - Mood disorders
    - Substance use disorders
    - Other mental disorders

N = 534; HNRC

Prevalence of major depressive disorder in people with HIV

More HIV risk behaviors and poorer ARV adherence in bipolar HIV infected persons

David Moore, et al., HNRP Group. Unpublished data
70% of HIV+ CHARTER participants have substance disorders

- Alcohol
- Cannabis
- Cocaine
- Opioids
- Amphetamines
- Hallucinogens
- Sedatives

CHARTER study. Unpublished data

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Management of HAND requires consideration of multiple mechanisms

- Antiretrovirals
- Reduce neurotoxins
- Reduce HIV replication in the CNS
- Improve neuroprotection
- Cognitive health

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Lower neurocognitive impairment risk when immunosuppression is avoided and virologic control is good

Heaton RK, et al. (2010). Neurology, 75, 2087-2096

CSF Viral Loads Are Associated with HAND When Compared to Plasma Viral Loads

Letendre et al, 17th CROI 2010, Abstract 172

Letendre et al, 16th CROI 2009, Abstract 484b
"Neuroeffective" ARV depends BOTH on CNS penetration AND antiviral potency

CNS Penetration Effectiveness Ranks 2010

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<td>Raltegravir</td>
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Extent of CSF penetration was 0.23% of plasma concentrations
Extents of CSF penetration was 1% of plasma concentrations


Letendre SL, et al. 17th CROI 2010, Abstract 172
Estimation of penetration-effectiveness in CNS
Better Penetration = Lower CSF viral loads

High CPE regimens related to greater likelihood of undetectable HIV in CSF vs plasma

Undetectable viral loads in the CSF (HIV < 2c/min) were noted in 46% - 53% of those receiving regimens with higher CPE (>8) scores, compared to 36% - 41% of those on lower rated CPE regimens.

Letendre SL, et al. 17th CROI 2010, Abstract 172
Individual ART from CHARTER Study (10% or more taking)

CHARTER, unpublished data

Most common combo regimens: Atripla (EFV/FTC/TBV) 22%
Boosted Atazanavir (ATV/RTV) and Truvada (FTC/TBV) 18%

CPE, CSF suppression, and NP change

<table>
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Ellis et al. Annual Meeting American Neurological Association 2009
Conceptual therapeutic window in the nervous system

Model courtesy of S. Letendre, Copyright S. Letendre

HNRP Recommendations

- **Question** patients about cognitive symptoms and activities of daily living at routine visits and before initiating ART
  - Brief testing improves the ability to correctly identify HAND
  - Screen for and treat other conditions that could account for nervous system complaints (e.g. co-infections, substance use, mood disorders, vascular disease, metabolic disorders)
  - Consider lumbar puncture and neuroimaging

- **Consider using ART with higher CPE** since accumulating data support that it better reduces HIV in CSF and leads to neurocognitive improvements

- **Continue to monitor** effectively treated patients
  - Cognitive impairment might persist or even occur for the first time in treated individuals: drug resistance and/or drug neurotoxicity?

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Approach to antiretroviral therapy

**HAND – off ART**
- Initiation of ART with a more neuroeffective regimen?
  - Most strongly supported scenario
  - Consistent findings from observational studies

**HAND – on ART**
- Switching or intensifying to a more neuroeffective regimen?
  - Concept supported by existing data
  - Must consider risk of failure and toxicity when changing therapy
  - No clinical trial yet being performed

**No Hand**
- Initiation of ART with a more neuroeffective regimen?
  - Indirectly supported by existing data
  - No clinical trial being performed
  - Treating all patients with CNS optimized ART may not be necessary

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EACS Recommended Screening for Neurocognitive Impairment

Any HIV-infected person complaining of disturbances in his/her memory (comprehension, clarity or speed) should be evaluated extensively, including neurological examination, neuropsychological assessment, cerebrospinal examination and imaging of the brain

- **Patients without such symptoms that should be targeted for screening**
  - Uncontrolled HIV infection (detectable plasma HIV RNA)
  - Use of antiretroviral agents with limited CNS penetration
  - Low CD4 nadir (<200 cells/mm3)
  - Ongoing depression

- **Screening tool**
  - International HIV Dementia Scale (IHDS) ng ART

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*European AIDS Clinical Society, Guidelines, Prevention and Management of Non-Infectious Co-Morbidities*
EACS Recommendations for Treatment if Neurocognitive Impairment Detected

Any HIV-infected person complaining of disturbances in his/her memory (comprehension, clarity or speed) should be evaluated extensively, including neurological examination, neuropsychological assessment, cerebrospinal examination and imaging of the brain.

- **Interventions if neurocognitive impairment detected:**
  - If patient is not on ART:
    - Consider initiation of ART in which at least 2 drugs penetrate CNS
    - Consider risk for antiretroviral resistance if prior virological failure
  - If patient is already on ART:
    - Consider changing antiretroviral treatment to active drugs with better CNS penetration
    - Consider genotyping of plasma and CSF HIV RNA whenever feasible prior to changing ART

**Acknowledgements**

**UCSD HNRP (I. Grant, Director)**
- Scott Letendre
- Ron Ellis
- Bob Heaton
- Edmund Capparelli
- Brookie Best
- David Moore
- Hamp Atkinson

**CHARTER (I. Grant, PI)**
- David Clifford
- Justin McArthur
- Ned Sacktor
- Ann Collier
- Davey Smith
- Tom Marcotte
- Cris Achim
- Steven Woods
- Eliezer Masliah
- Mariana Cherny
- Allen McCutchan

**National Institutes of Health**
- ...Mental Health
- ...Drug Abuse
- ...Neurological Disorders and Stroke

**Pharma**
- Abbott Laboratories

Special Thanks to Dr. Scott Letendre

**European AIDS Clinical Society, Guidelines, Prevention and Management of Non-Infectious Co-Morbidities**