Antiretroviral Drug Penetration into the Central Nervous System
Implications for HIV Control

Scott Letendre, M.D.
Associate Professor of Medicine
University of California, San Diego

10 October 2008
British HIV Association Meeting
London, England

Acknowledgements

Study Volunteers

- National Institute of Mental Health
- National Institute on Drug Abuse
- National Institute of Neurological Disorders and Stroke
- HIV Neurobehavioral Research Center
  - Ronald Ellis
  - Allen McCutchan
  - Igor Grant
  - Steven Paul Woods
  - Mariana Cherner
  - Robert Heaton
Epidemiology of HAD
Declining Incidence

Incidence rate (per 1000 person-years)

Introduction of HAART

Calendar year

Sacktor N. J Neurol. 2002; 8(S2):115-121

Epidemiology of HAND
High Prevalence in 2008

Proportion Impaired

Overall 55%
41% Not Confounded

CNS HIV AntiRetroviral Therapy Effects Research Project, Years 2003-2007
Epidemiology of HAND
The ALLRT Study

- Prospective observational cohort study
- 1160 volunteers in ACTG clinical trials
- All received at least 3 antiretrovirals for at least 20 weeks
  - 50% were therapy-naive and 50% were experienced

**ALLRT**: ACTG Longitudinal Linked Randomized Trials
**ACTG**: AIDS Clinical Trials Group

High Prevalence in the ALLRT Study

<table>
<thead>
<tr>
<th>Impairment Type</th>
<th>Prevalent Impairment</th>
<th>N</th>
<th>Impaired</th>
<th>Unimpaired</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild impairment</td>
<td>1160</td>
<td>458 (39%)</td>
<td>702 (61%)</td>
<td></td>
</tr>
<tr>
<td>Mild to moderate impairment</td>
<td>1160</td>
<td>304 (26%)</td>
<td>856 (74%)</td>
<td></td>
</tr>
<tr>
<td><strong>Follow-Up Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained impairment</td>
<td>991</td>
<td>217 (22%)</td>
<td>774 (78%)</td>
<td></td>
</tr>
<tr>
<td><strong>Incident Impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impairment onset after normal performance</td>
<td>615</td>
<td>128 (21%)</td>
<td>487 (79%)</td>
<td></td>
</tr>
</tbody>
</table>
Real World Consequences of HAND

- Difficulty with finances and meal preparation
- Employment challenges
  - 5 times more likely to complain of problems at work
  - Twice as likely to be unemployed
- Impaired driving
- Worse medication adherence
- Shorter survival

Heaton et al, Psychosom Med 1994, 56: 8-17
Sevigny et al, Arch Neurol 2007, 64: 97-102

Antiretroviral Neuroeffectiveness
Structure of the Blood-Brain Barrier

Slide Courtesy Clinical Care Options
Antiretroviral Neuroeffectiveness
ARV Distribution to the Brain Can Be Limited

Antiretroviral Neuroeffectiveness
Conceptual Model

HIV proteins
Pro-inflammatory cytokines
Oxidative stress
Excitotoxins

Antiretrovirals
Reduce Neurotoxins
Reduce HIV Replication in the CNS
Cognition Improves

Antioxidants
Growth factors
Neural Progenitor Cells

Adequate Neuroprotection
CD4 Counts Influence the Relationship Between CSF and Blood Viral Loads

- Among 1,201 cross-sectional pairs, viral loads in CSF and blood were strongly correlated
  \( r = 0.70, p < 0.001 \)
- Among 355 cross-sectional visits not taking ART
  \( r = 0.60, p < 0.001 \)
- Interaction between blood viral loads and CD4 counts (\( \beta = 0.35, p = 0.001 \))

Antiretroviral Neuroeffectiveness

*Nadir CD4 Counts > ~250 and Normal Cognition*

- Antiretrovirals
  - Reduce Neurotoxins
  - Lymphoid-Derived
- CNS-Derived
  - Cognition Maintained
- Neuroprotection Maintained
Antiretroviral Neuroeffectiveness

Nadir CD4 Counts < ~250 or HAND

- Reduce Neurotoxins
- Improve Neuroprotection
- Penetrating Antiretrovirals
- Lymphoid-Derived
- CNS-Derived
- Cognition Improves

Drug Characteristics

Influence Its Distribution into the CNS

- Protein Binding
- Molecular Weight
- Lipophilicity
- Ionization
- Molecular pumps

- NRTIs > PIs ~ NNRTIs
- NRTIs > NNRTIs > PIs
- PIs ~ NNRTIs > NRTIs
- Tenofovir
- PIs, IIs: P-glycoprotein
  NRTIs: Organic anion transporters
Pharmacokinetics in CSF

**Most Abacavir Levels in CSF Exceed IC₅₀**

- Extent of CSF penetration was 36% of plasma concentrations

**Tenofovir Has Lower Concentrations in CSF**

- Best et al, 15th CROI 2008, Abstract 131
- Extent of CSF penetration was 5% of plasma concentrations
Pharmacokinetics in CSF
All Amprenavir Levels in CSF Exceed IC\textsubscript{50}

Extent of CSF penetration was 1.3% of plasma concentrations
Letendre et al, 16th CROI 2009, Submitted

Pharmacokinetics in CSF
Fewer Atazanavir Levels Exceed the IC\textsubscript{50}

Extent of CSF penetration was 1% of plasma concentrations
Best et al, 13th CROI 2006, Abstract 576
Pharmacodynamics in CSF
Lopinavir-rtv Alone Reduces HIV RNA in CSF

Letendre et al., Clinical Infectious Diseases, 2007

HIV Neurobehavioral Research Center

Pharmacodynamics in CSF
Reduction of HIV RNA in CSF


HIV Neurobehavioral Research Center
## Antiretroviral Neuroeffectiveness

### CNS Penetration-Effectiveness Rank

<table>
<thead>
<tr>
<th>Higher</th>
<th>Intermediate</th>
<th>Lower</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>Emtricitabine</td>
<td>Didanosine</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Lamivudine</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Zalcitabine</td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Efavirenz</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir/r</td>
<td>Atazanavir</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Indinavir/r</td>
<td>Atazanavir/r</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>Indinavir</td>
<td>Saquinavir</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir</td>
<td>Saquinavir/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tipranavir</td>
</tr>
<tr>
<td>Fusion inhibitors</td>
<td></td>
<td>Enfuvirtide</td>
</tr>
</tbody>
</table>

### Antiretroviral Neuroeffectiveness

### CNS Penetration-Effectiveness Rank

<table>
<thead>
<tr>
<th>1</th>
<th>0.5</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>Emtricitabine</td>
<td>Didanosine</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Lamivudine</td>
<td>Tenofovir</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Zalcitabine</td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Efavirenz</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir/r</td>
<td>Atazanavir</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Indinavir/r</td>
<td>Atazanavir/r</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>Indinavir</td>
<td>Saquinavir</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir</td>
<td>Saquinavir/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tipranavir</td>
</tr>
<tr>
<td>Fusion inhibitors</td>
<td></td>
<td>Enfuvirtide</td>
</tr>
</tbody>
</table>

HIV Neurobehavioral Research Center
**Antiretroviral Neuroeffectiveness**

**CNS Penetration-Effectiveness Rank**

- Higher CPE scores correlated with lower HIV RNA levels in CSF
  \[ r = -0.12, \ p = 0.008 \]

- Each unit decrease in CPE rank was associated with a 2.43-fold increase in the odds of having detectable CSF VL after accounting for plasma viral loads

**Use of More Sensitive Assay in CSF**

- 125 CSF specimens with HIV RNA ≤ 50 c/mL
- 50% had detectable HIV RNA in CSF with a more sensitive assay
  - LLQ 2.5 copies/mL
- Detectable HIV in CSF were associated with lower CPE ranks and worse neuropsychological performance


Letendre et al, 14th CROI, Abstract 369
**Antiretroviral Neuroeffectiveness**

*Update from CROI 2008*

**Better CPE Ranks were associated with...**

- Greater neuropsychological improvement after 12 and 24 weeks of ART (*Letendre et al, Abstract 68*)
- Better neuropsychological performance after a mean of 1.5 years (*Tozzi et al, Abstract 391*)
- Lower prevalence of HIV brain pathology in tissue from 392 autopsies (*Everall et al, Abstract 67*)
- Better survival in people with PML (*Gasnault et al, Abstract 386*)

---

**Drug Characteristics of Newer ARVs**

<table>
<thead>
<tr>
<th></th>
<th>Unbound</th>
<th>MW</th>
<th>Cmin</th>
<th>IC50</th>
<th>Est.</th>
<th>LogP</th>
<th>P-gp</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td>0.1%</td>
<td>435</td>
<td>393</td>
<td>0.6</td>
<td>0.7</td>
<td>&gt; 5</td>
<td>Yes</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>1%</td>
<td>366</td>
<td>200</td>
<td>0.4</td>
<td>4.9</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td><strong>Protease Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darunavir</td>
<td>5%</td>
<td>548</td>
<td>3,539</td>
<td>5.0</td>
<td>35.4</td>
<td>1.62</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Integrase Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>17%</td>
<td>444</td>
<td>107</td>
<td>7.0</td>
<td>2.6</td>
<td>0.49</td>
<td>Yes</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>-</td>
<td>448</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>CCR5 Antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>24%</td>
<td>514</td>
<td>117</td>
<td>0.3</td>
<td>100.3</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Vicriviroc</td>
<td>16%</td>
<td>650</td>
<td>199</td>
<td>0.3</td>
<td>106.1</td>
<td>0.04</td>
<td>No</td>
</tr>
</tbody>
</table>
Antiretroviral Neuroeffectiveness

Predictors of CSF Failure

Variable at First Visit | CSF Failure | Log-Rank | Wilcoxon
--- | --- | --- | ---
Current CD4 Count | < 200/µL | < 0.001 | < 0.001
Age | < 43 years | 0.003 | 0.004
Antidepressant Use | No Antidepressants | 0.003 | 0.002
Ethnicity | Black | 0.008 | 0.008
Months of ART Use | < 12 months | 0.056 | 0.06
NNRTI-PI Use | PIs | 0.11 | 0.14
Global Rating | ≤ 6 | 0.11 | 0.16
CPE Rank | < 7 | 0.08 | 0.15
First Regimen | | | |

Survival analysis of 338 subjects who...
- Were on ART at their cross-sectional visit
- Had undetectable CSF viral loads and
- Had at least one longitudinal visit

59 Failures
- Detectable CSF viral load
- Median 8 months

279 Did Not Fail
- Median 19 months

“Discordant” Resistance in CSF and Blood

Data from the CHARTER Study

- 195 unique CSF-plasma pairs studied
  - 185 pairs successfully sequenced, without evidence of PCR contamination
  - 100 pairs had resistance mutations in one or both compartments
- Among patients with resistance, 1/3 on current ART
  - Median Plasma HIV RNA 4.6 log10 c/ml (IQR 4.1-4.8)
  - Median CSF HIV RNA 3.5 log10 c/ml (IQR 3.1-4.0)
  - Median CD4 Count 355 cells/mm³ (IQR 207-532)
  - Median CD4 Nadir 256 cells/mm³ (IQR 136-398)

Slide courtesy of Joseph K. Wong
“Discordant” Resistance in CSF and Blood  
*Data from the CHARTER Study*

- 39/100 (39%) drug resistant pairs demonstrated discordant resistance
  - 19/39 (49%) mutations plasma > mutations CSF
  - 18/39 (46%) mutations CSF > mutations plasma
  - 2/39 (5%) had the same number of mutations in CSF and plasma but had different mutation patterns
- Among those who had drug resistance and were taking ART, 62% (20/32) had discordance

---

“Discordant” Resistance in CSF and Blood  
*Data from the CHARTER Study*

- Proportion of the 100 pts with any resistance who had discordant mutations by drug class
  - 25 had any PI mutations: 20 (80%) had discordance
  - 40 had any NRTI mutations: 17 (42%) had discordance
  - 80 had any NNRTI mutations: 16 (20%) had discordance
"Discordant" Resistance in CSF and Blood
Correlates of Discordant Resistance

<table>
<thead>
<tr>
<th>Correlation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current CD4 &lt; 200/µL</td>
<td>0.05</td>
</tr>
<tr>
<td>Nadir CD4 &lt; 200/µL</td>
<td>0.03</td>
</tr>
<tr>
<td>ARV Use @ Sampling</td>
<td>0.001</td>
</tr>
<tr>
<td>CSF HIV RNA &gt; median</td>
<td>N.S.</td>
</tr>
<tr>
<td>Plasma HIV RNA &gt; median</td>
<td>N.S.</td>
</tr>
<tr>
<td>NP Impairment (Global)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Antiretroviral Effectiveness
Model of Need for Neuroeffective ART

Increasing Need for Neuroeffective ART

Blood

CNS

Declining CD4 Nadir
Increasing Likelihood of NeuroAIDS
Conclusions

- HAND continues to be highly prevalent in domestic and international settings
  - Reduces ART adherence and survival
- ART distribution and effectiveness in the CNS varies substantially between drugs and between individuals
- ART that has better estimated neuroeffectiveness…
  - Better reduces HIV RNA in CSF
  - Improves - and may prevent - HAND
  - May benefit other CNS complications

Conclusions

- By better reducing HIV in the CNS and improving cognition in the substantial minority of individuals with HAND, antiretroviral drugs that have better neuroeffectiveness may…
  - Improve medical adherence
  - Reduce generation of antiretroviral resistance
  - Prolong duration of antiviral control
  - Extend survival
Future Research Questions

- Has the pathogenesis of HAND changed with ART?
- Are certain drug resistance mutations less neurovirulent?
- Are we now seeing Alzheimer’s type neurodegeneration in some individuals?
- Are NRTIs important for control of HIV in the brain?
  - Some NRTIs may be more active in macrophages than lymphocytes
- To what extent can immune recovery injure the brain?
- What are the benefits of initiating therapy with a more neuroeffective ART regimen?
  - Reduced incidence of cognitive impairment?
  - Improved duration of therapeutic success?
  - Improved survival?
- What are the benefits of switching from a less neuroeffective to a more neuroeffective ART regimen?
  - Are the benefits limited to those with more advanced immunosuppression or with cognitive impairment?

Fin
## Antiretroviral Neuroeffectiveness

### Studies Evaluating Effectiveness in CSF

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Design</th>
<th>N</th>
<th>Effect</th>
<th>Penetration Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinori</td>
<td>2005</td>
<td>C-S</td>
<td>63</td>
<td>Lower VL</td>
<td>No. of detectable</td>
</tr>
<tr>
<td>Letendre</td>
<td>2004</td>
<td>P</td>
<td>31</td>
<td>Lower VL</td>
<td>No. of penetrators</td>
</tr>
<tr>
<td>Eggers</td>
<td>2003</td>
<td>P</td>
<td>40</td>
<td>Similar VL</td>
<td>Multiple</td>
</tr>
<tr>
<td>Marra</td>
<td>2003</td>
<td>P</td>
<td>25</td>
<td>Similar VL</td>
<td>ZDV, IDV</td>
</tr>
<tr>
<td>Solas</td>
<td>2003</td>
<td>C-S</td>
<td>41</td>
<td>Similar VL</td>
<td>IDV</td>
</tr>
<tr>
<td>Antinori (a)</td>
<td>2002</td>
<td>C-S</td>
<td>75</td>
<td>Lower VL</td>
<td>IDV</td>
</tr>
<tr>
<td>Antinori (b)</td>
<td>2002</td>
<td>P</td>
<td>29</td>
<td>Lower VL</td>
<td>≥ 3 Penetrators</td>
</tr>
<tr>
<td>DeLuca (a)</td>
<td>2002</td>
<td>C-S</td>
<td>134</td>
<td>Similar VL</td>
<td>No. of penetrators</td>
</tr>
<tr>
<td>DeLuca (b)</td>
<td>2002</td>
<td>P</td>
<td>50</td>
<td>Lower VL</td>
<td>No. of penetrators</td>
</tr>
<tr>
<td>Lafeuillade</td>
<td>2002</td>
<td>C-S</td>
<td>41</td>
<td>Similar VL</td>
<td>IDV vs. LPV-r or NFV</td>
</tr>
<tr>
<td>Robertson</td>
<td>2002</td>
<td>C-S</td>
<td>98</td>
<td>Similar VL</td>
<td>No. of penetrators</td>
</tr>
<tr>
<td>Letendre</td>
<td>2001</td>
<td>C-S</td>
<td>1239</td>
<td>Lower VL</td>
<td>NNRTI- vs. PI-based</td>
</tr>
<tr>
<td>Gisolf</td>
<td>2000</td>
<td>P</td>
<td>27</td>
<td>Lower VL</td>
<td>SQV-r+d4T vs. SQV-r</td>
</tr>
<tr>
<td>Murphy</td>
<td>2000</td>
<td>P</td>
<td>27</td>
<td>Lower VL</td>
<td>APV-ZDV-3TC vs. APV</td>
</tr>
</tbody>
</table>

### Penetration Measure

- **No. of detectable**
- **No. of penetrators**
- **Multiple**
  - ZDV, IDV
  - IDV
  - ≥ 3 Penetrators
  - IDV vs. LPV-r or NFV
  - No. of penetrators
  - NNRTI- vs. PI-based
  - SQV-r+d4T vs. SQV-r
  - APV-ZDV-3TC vs. APV
### Antiretroviral Neuroeffectiveness Studies Evaluating Cognitive Effectiveness

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Design</th>
<th>N</th>
<th>Effect</th>
<th>Penetration Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giancola</td>
<td>2006</td>
<td>C-S</td>
<td>165</td>
<td>Similar Global Performance</td>
<td>¹ 1, ² 2, ³ 3 Penetrators</td>
</tr>
<tr>
<td>Antinori</td>
<td>2004</td>
<td>C-S</td>
<td>165</td>
<td>Similar Global Performance</td>
<td>No. of Penetrators</td>
</tr>
<tr>
<td>Cysique</td>
<td>2004</td>
<td>P</td>
<td>97</td>
<td>Improved Learning, Recall &amp; Motor</td>
<td>³ 3 Penetrators</td>
</tr>
<tr>
<td>Evers (a)</td>
<td>2004</td>
<td>C-S</td>
<td>306</td>
<td>Improved Choice Reaction Times</td>
<td>Multiple</td>
</tr>
<tr>
<td>Evers (b)</td>
<td>2004</td>
<td>P</td>
<td>110</td>
<td>Similar Visual Evoked Potentials</td>
<td>Multiple</td>
</tr>
<tr>
<td>Letendre</td>
<td>2004</td>
<td>P</td>
<td>31</td>
<td>Similar Global Performance</td>
<td>No. of Penetrators</td>
</tr>
<tr>
<td>Robertson</td>
<td>2004</td>
<td>P</td>
<td>29</td>
<td>Similar Global Performance</td>
<td>No. of Penetrators</td>
</tr>
<tr>
<td>Chang</td>
<td>2003</td>
<td>P</td>
<td>33</td>
<td>Similar Performance &amp; MRS</td>
<td>² 2 Penetrators</td>
</tr>
<tr>
<td>Marra</td>
<td>2003</td>
<td>P</td>
<td>25</td>
<td>Improved Global Performance</td>
<td>ZDV, IDV</td>
</tr>
<tr>
<td>Dougherty</td>
<td>2002</td>
<td>P</td>
<td>96</td>
<td>Similar MSK Improvement</td>
<td>Single vs. Multiple</td>
</tr>
<tr>
<td>von Giesen</td>
<td>2002</td>
<td>P</td>
<td>104</td>
<td>Improved Psychomotor Speed</td>
<td>NVP vs. EFV</td>
</tr>
<tr>
<td>Sacktor</td>
<td>2001</td>
<td>P</td>
<td>73</td>
<td>Similar Psychomotor Performance</td>
<td>Single vs. Multiple</td>
</tr>
</tbody>
</table>
Pharmacodynamics and Cognition

**Improvement of NP Performance**

\[ \chi^2 = 6.3; P = 0.01 \]

Not Suppressed N=14

Suppressed N=17


**Risk Factors for HAND**

**Host**
- AIDS, Malnutrition
- Anemia, Thrombocytopenia
- Age, Gender
- Insulin Resistance
- Stimulants
  - Methamphetamine
  - Cocaine
- Genetics
- Chemokines

**Viral**
- Genetics
- Clade-Subtype
- Neuroadaptation
- Resistance
- Co-pathogens
- Hepatitis C
Risk Factors for HAND

**Host**
- AIDS
- Malnutrition
- Anemia
- Thrombocytopenia
- Age
- Gender
- Insulin Resistance
- Stimulants
  - Methamphetamine
  - Cocaine
- Genetics
- Chemokines

**Viral**
- Genetics
- Clade-Subtype
- Neuroadaptation
- Resistance
- Co-pathogens
- Hepatitis C

Valcour et al, JAIDS, 2006, 43: 405-10
Chemer et al, Neurology, 2005, 64: 1343-7
Gonzalez et al, PNAS, 2002, 99: 13795-800
Letendre et al, J Infect Dis, 2007, 196: 361-70
Hightower et al, 15th CROI, 2008

Consequences of HAND

**Shorter Survival**

Ellis RJ et al, Arch Neurol, 1997
Screening Assessments
ALLRT Brief NeuroScreen

- Trailmaking (A&B)
- WAIS-R Digit Symbol task
- Requires < 15 min


Screening Assessments
International HIV Dementia Scale

- Memory-Registration: Word Recall
- Motor Speed: Finger tapping
- Psychomotor Speed: Alternating hand movements

IHDS Score
Maximum score is 12 points
Score of ≤ 10: Possible dementia

Antiretroviral Effectiveness
CNS Penetration-Effectiveness Rank

<table>
<thead>
<tr>
<th>Drug Characteristics</th>
<th>Concentrations Exceed the Wild-type IC50</th>
<th>Effectiveness in Clinical Studies</th>
<th>Estimated Neuro-Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substantial Penetration</td>
<td>Consistently Independent</td>
<td>Higher</td>
<td></td>
</tr>
<tr>
<td>Marginal Penetration</td>
<td>Inconsistently Not clearly independent</td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>Poor Penetration</td>
<td>Rarely Ineffective</td>
<td>Lower</td>
<td></td>
</tr>
</tbody>
</table>

Letendre et al, 13th CROI, 2006, Abstract 74

Epidemiology of HAND
High Prevalence in Resource Limited Settings

Proportion Impaired

Chennai India 56%
Pune India 47%
Anhui China 37%
Bangkok Thailand 33%
Kampala Uganda 31%
APNAC 12%
ACTG 5%