Acknowledgements & Conflicts

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U.S. National Institutes of Health
Measuring Cognitive Changes in HIV Infection: Size Really Matters

Jose A. Muñoz-Moreno, Ph.D.
Lluita contra la SIDA Foundation
Germans Trias i Pujol University Hospital
Badalona, Barcelona
Catalonia, Spain
Measuring Cognitive Change in HIV Population

Updated research nosology for HIV-associated neurocognitive disorders

Neuropsychological (NP) Testing is available:

Asymptomatic Neurocognitive Impairment (ANI)

NIH definition: in 3 cognitive domains that cannot be explained by opportunistic CNS disease, systemic illness, psychiatric illness, substance use disorders, or medications with CNS effects.

Mild Neurocognitive Disorder (MND)

NIH definition: 1 SD below a demographically appropriate normative mean, involving ≥2 cognitive domains.

HIV-Associated Dementia (HAD)

> Moderate HIV impairment +1.5 SD below a demographically appropriate normative mean on ≥2 cognitive domains.

Measuring Cognitive Change in Non-HIV Population

Neurocognitive Function in HIV-Infected Patients: Comparison of Two Methods to Define Impairment

Psychometric Performance: Test Scores on Computerized Testing (1)

Selected Tests:

- Digit Symbol Substitution Test (SSD)
- Trail Making Test (TM), Parts A & B
- Stroop Test
- Category Test
- CogState Battery
- Digit Attention Test
- New Subjective Memory Questionnaire

Measuring Cognitive Change in Non-HIV Population


5. The use of normative data to adjust for demographic/nectodemographic factors is essential for the correct interpretation of standard neuropsychological tests with quantitative outcomes. The standard reference books (Hedden et al., 2006; Sack et al., 2005; Strauss et al., 2006) state that the neuropsychologist will also use qualitative information (for example level of motivation, level of reading or writing proficiency, etc.) and contextual the quantitative results.

- In developing and developed countries the effects of age, education, and gender (as well as ethnicity in some countries) must be considered.
- Geographic characteristics (such as coming from an urban versus rural environment) may need to be considered in addition to the traditional demographic factors in developing countries. The standard reference books (Hedden et al., 2006; Sack et al., 2005; Strauss et al., 2006)
- Normative data should be selected to best represent the demographic reference for a particular participant. In some instances, test norms based on a smaller sample size are recommended over non-local norms based on large sample sizes. The standard reference books (Strauss et al., 2006)
Practice Effect

Normative data and validation of a regression based summary score for assessing meaningful neuropsychological change

Lucette A. Csapo1,2, Donald Franklin, Jr.3, Ian Abramone2, Ronald J. Ellis1, Scott Lecomte4, Alain Collard5, David CBricot6, Benjamin Calmettes7, Justin McCarthy8, Susan Mergiel9, David Simpson1, Alix Mccatchell1, Igor Grant1, Robert K. Hrazdira1, the CHARTER group, and the HNRC group.

JOURNAL OF CLINICAL AND EXPERIMENTAL NEUROPSYCHOLOGY 2011, 351, 303-312

Examples of Studies (5)

Dynamics of cognitive change in HIV-infected individuals commencing three different initial antiretroviral regimens: a randomized, controlled study

Winston et al., HIV Medicine, 2012

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Winston et al / 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design / Sample</td>
<td>Randomized, Open-Label / N = 28</td>
</tr>
<tr>
<td>Intervention</td>
<td>LAMT (FTC + 11 EFV, 21 ATV(1, 3) AZT(D4T)</td>
</tr>
<tr>
<td>Efficacy Endpoint</td>
<td>NP2D / 3 domains</td>
</tr>
<tr>
<td>Time</td>
<td>24 weeks + 48 weeks</td>
</tr>
<tr>
<td>Statistical Approach</td>
<td>1 test, p values</td>
</tr>
<tr>
<td>Results</td>
<td>Significant improvements</td>
</tr>
</tbody>
</table>
### Rivastigmine for HIV-associated neurocognitive disorders

A randomized crossover pilot study

Simioni et al, Neurology, 2013

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autor / Year</strong></td>
<td>Simioni et al / 2013</td>
</tr>
<tr>
<td><strong>Design / Sample</strong></td>
<td>Cross-over, Pilot/ N = 17</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Rivastigmine</td>
</tr>
<tr>
<td><strong>Efficacy Endpoint</strong></td>
<td>Specific scores / 5 domains</td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td>20 weeks</td>
</tr>
<tr>
<td><strong>Statistical Approach</strong></td>
<td>ANOVA, p values</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>No significant improvement</td>
</tr>
</tbody>
</table>
Neurological Soft signs in HIV associated neurocognitive disorder (HAND):
an easy clinical examination for screening and early recognition

Johannes Schröder, Christina Herold and Pablo Toro
Section for Geriatric Psychiatry, Ruprecht- Karls Universität Heidelberg
Dept. of Psychiatry, Pontificia Universidad Católica de Chile
Neurological soft signs

- comprise both, minor motor and sensory abnormalities
- are frequently found in major psychiatric disorders
- vary in the clinical course
- can be reliably assessed by using rating scales, such as the Heidelberg scale as part of the routine work up

Heidelberg Scale Subscale and Test

1. Motor coordination
   Ozeretki's test
   Diadochokinesis
   Pronation/supination
   Finger/thumb opposition
   Articulation
2. Sensory integration
   Gait
   Tandem gait
   2-point discrimination
3. Complex motor tasks
   Finger-to-nose test
   Fist-edge-palm test
4. Right/left and spatial orientation
   Right/left orientation
   Graphesthesia
   Face/hand sensory test
   Stereognosis
5. Hard signs
   Arm-holding test
   Mirror movements

Heidelberg NSS-Scale

- Three point rating scale
  (max. 81 points)
- High internal consistency
  Cronbach's α: 0.85/0.89
- Test-retest reliability
  r=0.80, p<0.001
- Interrater reliability
  r=0.88, p<0.005

Schröder et al., 1992
Bachmann et al., 2005
Valenzuela et al., 2014
NSS subscales

* $p < 0.05$
Preliminary study of a novel cognitive assessment device for the evaluation of HIV-associated neurocognitive impairment

Albert M. Anderson¹ · Jeffrey L. Lennox¹ · Minh L. Nguyen¹ · Drenna Waldrop-Valverde¹ · William R. Tyor¹ · David W. Loring¹

DOI 10.1007/s13365-016-0458-z
Questions for Consideration

• What standardized methods should be used to ensure comparability between trials?
  • Neuropsychological testing, NSS, imaging, biomarkers
  • How often should participants be assessed?
  • For how long should participants be followed?
• The Frascati guidelines are a decade old. Should they be updated considering 10 years of progress?
• What are the most promising interventions now?
  • Changing “habits”: Exercise, diet
  • Treating comorbid disease: depression, substance use, sleep disorders, metabolic and vascular disease
  • Adjunctive therapies: rivastigmine, paroxetine
Pros and Cons of antiretroviral treatment on CNS

Ignacio Pérez Valero
Hospital U. La Paz
Intensity of CNS disease is not always the same

Current regimens have enough CNS penetration

Uncommon & transient

And it is not associated with NP decline

In-vitro neurotoxicity is associated to drug levels

Does Changing CSF Pharmacology Over Time Influence CNS Adverse Events?

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Week 2</th>
<th>Week 16</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG Plasma, total*</td>
<td>3360</td>
<td>3210</td>
<td>-4.5%</td>
</tr>
<tr>
<td>DTG Plasma, unbound*</td>
<td>17.1</td>
<td>23.9</td>
<td>+39.8%</td>
</tr>
<tr>
<td>DTG CSF, total*</td>
<td>18.2</td>
<td>13.2</td>
<td>-27.5%</td>
</tr>
<tr>
<td>CSF–total plasma ratio, %</td>
<td>0.516</td>
<td>0.412</td>
<td>-20.2%</td>
</tr>
</tbody>
</table>

*ng/mL
All values are medians

**Notes:**
- Pozniak et al, Lancet Infectious Disease 2014; 14: 590–99

**Graphs:**
- Graph A: Changing CSF pharmacology over time.
- Graph B: Comparison of patients with adverse events between switch and no-switch groups.
We need ART to be balanced

Risk of Brain Injury

Drug Resistance

HIV-Mediated Immune-Mediated

ART Therapeutic Threshold

Symptomatic Threshold

Neurotoxicity Threshold

Unclear Clinical Significance

ART Concentrations in the CNS

Personal Slide Courtesy of S. Letendre
Questions for Consideration

• Do current ART regimens have sufficient potency outside and inside the CNS to minimize the effects of HIV replication?
  • Will we continue to see CSF viral escape?

• How will the clinical environment shift over the next 5 years (long-acting ART, new classes of drugs)

• How will we control inflammation from low-level replication and production of neurotoxic HIV proteins?

• How do we implement neurotoxicity data into the clinic?

• Will we need different treatment strategies for patients with different characteristics (e.g., aged)?
Integrase inhibitors and the brain

Professor Alan Winston
St. Mary’s Hospital London
May 2017

Disclaimer:
Gilead Sciences Europe Ltd has provided the funding for this session
The presentation express the views and opinion of the presenter which are based on information and data available at the time
The history of EFV-associated CNS toxicities


IDV, indinavir; NVP, Nevirapine, PI, protease inhibitor; SBR, stable baseline regimen; RAL, raltegravir; MVC, maraviroc; LPV, lopinavir; ATV, atazanavir; ETR, etravirine; RTV, ritonavir; EFV, efavirenz; Comp, comparator

n's represent no. of EFV patients

% Patients with Any Neuropsychiatric Event
# How long does it take to identify a problem?

<table>
<thead>
<tr>
<th>Drug/class</th>
<th>FDA approval</th>
<th>Toxicity</th>
<th>Signal</th>
<th>Delay (years)</th>
<th>Risk (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>stavudine¹</td>
<td>1994¹⁴</td>
<td>Lipoatrophy</td>
<td>1999⁷</td>
<td>5</td>
<td>RR 1.95 (1.18-3.22)</td>
</tr>
<tr>
<td>nevirapine²</td>
<td>1996¹⁴</td>
<td>Toxicity at high CD4</td>
<td>2005⁸</td>
<td>9</td>
<td>Female 12 x higher risk Male 5 x higher risk</td>
</tr>
<tr>
<td>PIs</td>
<td>1996¹⁴</td>
<td>Heart attack</td>
<td>2003⁹</td>
<td>7</td>
<td>RH 2.56 (1.03-6.34)</td>
</tr>
<tr>
<td>efavirenz³</td>
<td>1998¹⁴</td>
<td>Suicidality</td>
<td>2013¹⁰</td>
<td>15</td>
<td>HR 2.28 (1.27,4.10)</td>
</tr>
<tr>
<td>abacavir⁴</td>
<td>1998¹⁴</td>
<td>Heart attack</td>
<td>2008¹¹</td>
<td>10</td>
<td>RR 1.14 (1.08–1.21)</td>
</tr>
<tr>
<td>tenofovir⁵</td>
<td>2001¹⁴</td>
<td>Fracture</td>
<td>2012¹²</td>
<td>11</td>
<td>HR 1.080 (1.02,1.15)</td>
</tr>
<tr>
<td>Raltegravir⁶</td>
<td>2007¹⁴</td>
<td>Myopathy</td>
<td>2013¹³</td>
<td>5</td>
<td>OR 2.64 (1.57-4.45)</td>
</tr>
</tbody>
</table>

Pis, Protease Inhibitors; RR, Relative risk; RH, Relative hazard; HR, Hazard ratio; OR, overall risk

¹. Stavudine SPC [https://www.medicines.org.uk/emc/medicine/21122](https://www.medicines.org.uk/emc/medicine/21122)  
². Nevirapine SPC [https://www.medicines.org.uk/emc/medicine/322](https://www.medicines.org.uk/emc/medicine/322)  
³. Efavirenz SPC [https://www.medicines.org.uk/emc/medicine/11284](https://www.medicines.org.uk/emc/medicine/11284)  
⁴. Abacavir SPC [https://www.medicines.org.uk/emc/medicine/2476](https://www.medicines.org.uk/emc/medicine/2476)  
⁵. Tenofovir SPC [https://www.medicines.org.uk/emc/medicine/9008](https://www.medicines.org.uk/emc/medicine/9008)  
⁶. Raltegravir SPC [https://www.medicines.org.uk/emc/medicine/20484](https://www.medicines.org.uk/emc/medicine/20484)  
Neurotoxicity May Be Masked in the Early Treatment Period

# Dolutegravir cohort data

<table>
<thead>
<tr>
<th>Clinic</th>
<th>No. of patients</th>
<th>d/c due to AEs n (%)</th>
<th>Main reasons for d/c</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLVG</td>
<td>387</td>
<td>62 (16%)</td>
<td>Sleeping, gastro-intestinal, neurological</td>
</tr>
<tr>
<td>Brighton</td>
<td>128</td>
<td>16 (13%)</td>
<td>Sleep</td>
</tr>
<tr>
<td>Foch</td>
<td>105</td>
<td>11 (10.4%)</td>
<td>Vertigo, headache, insomnia, malaise</td>
</tr>
<tr>
<td>Cardiff</td>
<td>63</td>
<td>6 (10%)</td>
<td>Sleep</td>
</tr>
<tr>
<td>Manchester</td>
<td>178</td>
<td>15 (8.4%)</td>
<td>CNS, malaise and joint pain</td>
</tr>
<tr>
<td>Cologne</td>
<td>985</td>
<td>67 (6.8%)</td>
<td>Neuropsychiatric (5.0%), gastro-intestinal (0.7%), skin (0.3%), renal (0.2%), hepatic (0.1%)</td>
</tr>
<tr>
<td>St Thomas</td>
<td>181</td>
<td>9 (5%)</td>
<td>Insomnia, malaise/myalgia</td>
</tr>
<tr>
<td>DOL-ART</td>
<td>411</td>
<td>18 (4.4%)</td>
<td>Depression (1.2%), GI symptoms (1%)</td>
</tr>
<tr>
<td>Ramon Y Cajal</td>
<td>827</td>
<td>36 (4.3%)</td>
<td>Headache, dyslipidemia, insomnia, dizziness, mood disorders</td>
</tr>
<tr>
<td>Cruser Kobler AIDS centre</td>
<td>73</td>
<td>3 (4.1%)</td>
<td>CNS (2), gastro-intestinal (1) 19% patients had AEs, and 11% CNS AEs</td>
</tr>
<tr>
<td>Liverpool</td>
<td>178</td>
<td>8 (4%)</td>
<td>n/a, 33% have AEs of whom 20% CNS, 10% gastrointestinal, 7% neurological, 3% musculoskeletal, 3% lethargy</td>
</tr>
<tr>
<td>Llibre</td>
<td>873</td>
<td>25 (3%)</td>
<td>Neuropsychiatric toxicity definition included anxiety, depression, insomnia, dizziness, nightmares, paresthesia, somnolence, tremor and vertigo (adjusted HR of 3.18 DTG vs RAL &amp; 4.93 DTG vs EVG/COBI)</td>
</tr>
<tr>
<td>Imperial</td>
<td>138</td>
<td>3 (2%)</td>
<td>Sleep dizziness</td>
</tr>
<tr>
<td>Osaka</td>
<td>101</td>
<td>n/a</td>
<td>20.8% reported CNS AEs: headache (7.9%), insomnia (5.9%)</td>
</tr>
</tbody>
</table>

d/c: discontinuation; AE: adverse events; CNS: central nervous system

## CNS Safety Data from Dolutegravir Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>SPRING-1&lt;sup&gt;1&lt;/sup&gt;</th>
<th>SPRING-2&lt;sup&gt;2&lt;/sup&gt;</th>
<th>FLAMINGO&lt;sup&gt;3&lt;/sup&gt;</th>
<th>SINGLE&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG n=51 EFV n=50</td>
<td>DTG n=411 RTG n=411</td>
<td>DTG n=242 DRV/r n=242</td>
<td>DTG n=357 EFV n=362</td>
</tr>
<tr>
<td>Headache</td>
<td>10% 4%</td>
<td>14% 13%</td>
<td>17% 11%</td>
<td>6% 7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6% 18%</td>
<td>6% 6%</td>
<td>6% 5%</td>
<td>7% 33%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6% 10%</td>
<td>6% 5%</td>
<td>8% 7%</td>
<td>10% 6%</td>
</tr>
<tr>
<td>Depression</td>
<td>* *</td>
<td>6% 5%</td>
<td>6% 4%</td>
<td>** **</td>
</tr>
<tr>
<td>Anxiety</td>
<td>* *</td>
<td>4% 5%</td>
<td>5% 4%</td>
<td>** **</td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>* *</td>
<td>** **</td>
<td>** **</td>
<td>7% 16%</td>
</tr>
</tbody>
</table>

* < 3%  
** < 5%

All data are from 96 weeks

<sup>1</sup>Stellbrink et al, AIDS 2013, 27:1771–1778  
<sup>2</sup>Raffi et al, Lancet 2013, 13: 927–35  
<sup>4</sup>Walmsley et al, JAIDS 2015, 70:515–519
# CNS Safety Data from Elvitegravir Clinical Trials

## Summary

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Study 102&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Study 103&lt;sup&gt;2&lt;/sup&gt;</th>
<th>STRATEGY-NNRTI&lt;sup&gt;3&lt;/sup&gt;</th>
<th>STRATEGY-PI&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVG/c n=348</td>
<td>EFV n=352</td>
<td>EVG/c n=353</td>
<td>ATV/r n=355</td>
</tr>
<tr>
<td>Headache</td>
<td>16%</td>
<td>11%</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7%</td>
<td>26%</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11%</td>
<td>16%</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Depression</td>
<td>12%</td>
<td>14%</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>15%</td>
<td>28%</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Back Pain</td>
<td>*</td>
<td>*</td>
<td>12%</td>
<td>5%</td>
</tr>
</tbody>
</table>

* < 10%

** < 5%

---

<sup>1</sup>Zolopa et al, JAIDS 2013, 63: 96–100

<sup>2</sup>Rockstroh et al, JAIDS 2013, 62: 483–486

<sup>3</sup>Pozniak et al, Lancet Inf Dis 2014; 14: 590–99

<sup>4</sup>Arribas et al, Lancet Inf Dis 2014, 14: 581–89
Pharmacokinetic considerations

Evaluation of association of DTG concentration and CNS side effects in 162 HIV-infected patients on DTG in Osaka, Japan, Apr 2014 to Mar 2016

DTG Plasma-Trough Concentration in Patients with CNS AEs

Patients with CNS AEs (%)

Quartile 1 (≤0.75 µg/mL)  Quartile 2 (0.75-1.07 µg/mL)  Quartile 3 (1.08-1.47 µg/mL)  Quartile 4 (>1.47 µg/mL)

"A positive correlation between DTG plasma trough concentration and CNS side effects was identified in a Japanese population."

The contribution of abacavir

Intolerance in regimens in

Proportion of patients on DTG

Total days on DGV containing regimen
Neurotoxicity Screening of ART Drugs With Human iPSC-Derived Neurons

<table>
<thead>
<tr>
<th></th>
<th>Mitochondrial Assay</th>
<th>Neurite Outgrowth Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMP</td>
<td>ROS</td>
</tr>
<tr>
<td>NRTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>1.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>1.6</td>
<td>0.0</td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>-13.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>-6.2</td>
<td>1.0</td>
</tr>
<tr>
<td>INSTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>-10.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>-2.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Darunavir</td>
<td>2.1</td>
<td>0.4</td>
</tr>
<tr>
<td>PK enhancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>-5.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Cobicistat</td>
<td>-12.0</td>
<td>7.7</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menadione</td>
<td>-12.0</td>
<td>10.6</td>
</tr>
<tr>
<td>Staurosporine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIO</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Max. Z-score

-5 5

Hinckley et al, CROI 2016, Abstract 395
Questions for Consideration

• Do neuropsychiatric adverse events occur with both dolutegravir and elvitegravir?
  – Will bictegravir also have neuropsychiatric side effects?
  – Is raltegravir an attractive alternative for initial therapy for patients with risk factors or for switching when AEs occur?

• What is the contribution of other risk factors (e.g., abacavir, age, sex)?

• If symptoms subside but drug is continued, will cumulative injury occur with resulting long-term cognitive or mood disorders?
  – If they do, will they be reversible?
Pharmacokinetic Issues and CNS in HIV-infected Patients

Andrea Calcagno
University of Torino, Italy
Summary of PK and CSF/CNS outcomes

- CSF HIV RNA < 50 copies/mL
- Several cofactors

- CSF HIV RNA < 0.5-2 copies/mL
- duration of treatment

- Asymptomatic CSF escape
- LLV?

- Symptomatic CSF escape
- Nadir CD4, RAMS1

- NC Function
- Several cofactors

Penetrazione omogenea?

Brain tissue concentrations

A. Simulated plasma concentration of efavirenz
B. Simulated concentration of efavirenz in CSF
C. Simulated concentration of efavirenz in brain

**Predicted Cmax**
- plasma: 3184 ng/mL (2219 - 485)
- CSF: 49.9 ng/mL (36.6 - 69.7)
- brainT: 50343 ng/mL (38351 - 65799)
- tissue to plasma ratio = 15.8

**Observed Cmax - rats**
- plasma: 69.7 ng/mL (44.9 – 130.6)
- brainT: 702.9 ng/mL (475.5 - 1018)
- tissue to plasma ratio = 9.5 (7-10.9)
ART Drug Concentrations in Brain: Regional Variation, CSF Comparability

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration Region</th>
<th>Overall Mean (ng/mL)</th>
<th>WM mean (ng/mL)</th>
<th>GP mean (ng/mL)</th>
<th>CGM mean (ng/mL)</th>
<th>CSF (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concentrations Similar to Historical CSF Concentration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir (ATV)</td>
<td>2</td>
<td>&lt; 25</td>
<td>&lt; 25</td>
<td>&lt; 25</td>
<td>&lt; 25</td>
<td>10.3(^1)</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>2</td>
<td>38.6</td>
<td>45.2</td>
<td>34.8</td>
<td>35.9</td>
<td>15.6(^2)</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>4</td>
<td>181.3</td>
<td>230.4</td>
<td>173.2</td>
<td>140.3</td>
<td>109.0(^3)</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>3</td>
<td>196.9</td>
<td>205.5</td>
<td>209.8</td>
<td>175.4</td>
<td>107.8(^4)</td>
</tr>
<tr>
<td><strong>Concentrations in White Matter Higher than Historical CSF Concentration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir (LPV)</td>
<td>4</td>
<td>153.3</td>
<td>410.6</td>
<td>&lt; 25</td>
<td>&lt; 25</td>
<td>16.8(^5)</td>
</tr>
<tr>
<td><strong>Concentrations Higher than Historical CSF Concentration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td>6</td>
<td>206.0</td>
<td>220.0</td>
<td>212.1</td>
<td>185.8</td>
<td>5.5(^6)</td>
</tr>
</tbody>
</table>

WM = White Matter; GP = Globus Pallidus (Deep Gray Matter); CGM = Cortical Gray Matter

Across all drugs, concentrations were lower in CGM than in the other two regions (p=0.01, paired signed rank test)

Bumpus et al, CROI 2015, Abstract 436
CSF-Serum Albumin Ratio is Associated with Lipids, Cannabis, and ART Concentrations
Symptomatic CSF escape

Two case series and few case reports  
\( n=30 \)

- Acute neurological symptoms
- Resistance associated mutations
- MRI alterations
- Strong immune response
- Reversibility

---

<table>
<thead>
<tr>
<th>Drug</th>
<th>CPE score</th>
<th>95% inhibitory concentration</th>
<th>Macrophage efficacy score</th>
<th>in vitro neurotox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>3</td>
<td>NA</td>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>3</td>
<td>NA</td>
<td>12.5</td>
<td>0</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>2</td>
<td>NA</td>
<td>50</td>
<td>+</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>1</td>
<td>NA</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>4</td>
<td>NA</td>
<td>50</td>
<td>+</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>4</td>
<td>NA</td>
<td>20</td>
<td>+</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>3</td>
<td>6.4</td>
<td>100</td>
<td>++</td>
</tr>
<tr>
<td>Etravirine</td>
<td>2</td>
<td>5.1</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>37</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>2</td>
<td>0.4</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Atazanavir/rt</td>
<td>2</td>
<td>2.8</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Darunavir/rt</td>
<td>3</td>
<td>1.8-18.5</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Lopinavir/rt</td>
<td>3</td>
<td>1.5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>3</td>
<td>0.7</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Evitegravir/rt</td>
<td>37</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
</tr>
<tr>
<td>Dolastavir</td>
<td>47</td>
<td>NA</td>
<td>NA</td>
<td>+?</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>1</td>
<td>NA</td>
<td>50</td>
<td>NA</td>
</tr>
</tbody>
</table>

---

CSF Viral Escape May Be Associated with Depression

Hammond et al, J Neurovirol 2016, PMID: 26727907
Questions for Consideration

• Do CNS drug characteristics and pharmacokinetics matter in the management of antiretroviral therapy?
• How does CSF pharmacology vary over time?
• Are CSF drug concentrations an adequate surrogate for brain tissue concentrations?
• Is CSF viral escape a clinically important entity?
  – Does it influence risk for other neuropsychiatric disorders?
• Are the factors that influence CSF pharmacology too complex to integrate into patient care?
NEUROTICISM AND ITS INFLUENCE ON ANTIRETROVIRAL THERAPY

10th Symposium on Neuropsychiatry and HIV

Dr. Daniel Hernández Huerta
Psychiatry Department
Ramon y Cajal University Hospital
Madrid, Spain

HIV awareness in young population: Differences between HIV positive young adults infected due to vertical transmission and their HIV-negative peers. NeurocoRISpe and FARO projects


Relationship between methadone therapeutic use and adherence to antiretroviral therapy in Spain

Carlos Parro Torres
Hospital General Universitario Gregorio Marañón
Madrid, Spain
Management of a HIV-infected patient with a psychiatric disorder

Maria Ferrara, Modena, Italia
Guida Da Ponte, Lisboa, Portugal
Jordi Blanch, Barcelona

HIV and the Central Nervous System – Diagnosing HAND

- Gabriele Arendt
- Dept. of Neurology, University of Duesseldorf, Medical Faculty
- 10th International Symposium on Neuropsychiatry & HIV, Barcelona, May 26-27th, 2017

Practical training on diagnosis and management of clinical CNS problems in HIV-infected patients

Prevention of neurocognitive impairment in HIV-infected patients

Paola Cinque
Department of Infectious Diseases
San Raffaele Scientific Institute, Milano, Italy

Workshop. Practical Training on diagnosis and management of clinical CNS problems in HIV-positive individuals

Treatment

Alan Winston  Andrea Calcagno
Neuropsychiatric consequences of substance use

Jordi Blanch

Hospital Clínic de Barcelona
Parc Sanitari Sant Joan de Déu
Universitat de Barcelona
CIBERSAM
Alcohol and HIV

Methamphetamine

- CNS stimulant: euphoric, stimulating, aphrodisiac
- obtained: drugs marketed or clandestine laboratories
- white, crystalline, odorless and bitter powder
- smoking, inhaling, injecting or taking oral
- inhibits ejaculation
- Greater use in MSM
  - "Crystal", "crystal meth", "meth"

MSM using MA

- Increased risk of
  - Unprotected anal intercourse
  - Group sex
  - Having multiple sexual partners
  - Contact sexual partners online
  - Sexual relations with UDVP
  - Be intoxicated while keeping rrsbse
- Unrelated to the HIV- infection

Methamphetamine and VIH

- more consumption (20-30%) in MSM that are HIV + compared to HIV-
  (Buchacz et al., 2005, Forrest et al., 2010, Mansergh et al., 2006; Schwarz et al., 2007).
- higher VL (Ellis et al., 2003, Fairbairn et al., 2011, King et al., 2009, Feldman 2015)
- lower CD4 count (Shootaw et al., 2012)
- accelerates the progression of the disease (Carrico, 2011).
- increased risk of transmission (Cohen 2011)
- neurotoxic (Silverstein 2011)
- changes the BBB (Northrop 2015)
Spain's crystal-meth problem may be about to get worse (Business Insider 17 Nov 2016)

Spanish police broke up a drug ring smuggling methamphetamine using packages of chocolates, December 2014.

Lab equipment allegedly used to produce synthetic drugs recovered by Spanish police, September 2016
“Sex on drugs” (ChemSex): Psychosocial impact on the life of a group of gay, bisexual and other MSM from Barcelona City

Percy Fernández-Dávila, Ph.D
Drug use by HIV serostatus

Search for sex partners by apps
Mental health impact

Cuando yo cogía el metro, una paranoia de que toda la gente me está mirando, empezaba a sudar, y después no tenía ganas de salir de mi casa. Cuando empezaba a tomar más y más, no tenía ganas de salir de la casa, antes tenia esta paranoia, de que va a salir alguien del agujero de la puerta, que alguien hay del otro lado... Ahí pasas a no disfrutar más... ENT15, 44 años, latinoamericano.

Mental health harms: depression

Quedé con otro chico el sábado porque yo iba colocado el viernes, y como la tina te coloca mucho, le dije: “voy a follar contigo” y fue otra vez. Y luego estuve con una depresión durante la semana.

P: ¿Y cuánto te tomó recuperarte?
No me he recuperado todavía.
P: ¿De qué?
De la depresión, del ansia que provocó y todo, no estoy diciendo que ha sido la droga, pero ha sido el desencadenante de todo que a lo mejor tenía dentro. ENT17, 40 años, europeo.
Risk behavior, effect on HIV-infection and neuropsychiatric consequences of substance use

Maria Martínez-Rebollar
Hospital Clínic-Fundació Clínic
Barcelona
Increasing evidence of HIV, AHC, STIs and other complications associated with Chemsex use

- Associations with sexual-risk behaviour (Cotthus & Guzman, 2008; De Ryck, Van Laecke, Niewegiger, Pajos, & Collemboules, 2013; Chumming et al., 2017; Heiligeburg et al., 2012; Molley-Copson, Jents, & Swartz, 2014; Papas & Hamlis, 2011; Prestage et al., 2008; Smit & et al., 2015; Stoddard, 2017)

- Association with facilitation HIV: (Boschel et al., 2005; Macmillan et al., 2007; Pankey et al., 2007; Prestage et al., 2009; Grover et al., 2008)


- Potential risk of serious overdose and death (Hooker et al., 2017; Caldwell, Chow, Burns, Folkins, & Byrd, 2004; Licch & Kupferschmidt, 2004)

- Drug-drug interactions (Plowin, 2016; Bracho, 2015)

Incidence of HepC among HIV + MSM, 2000–2015

- Associations with sexual-risk behaviour (Cotthus & Guzman, 2008; De Ryck, Van Laecke, Niewegiger, Pajos, & Collemboules, 2013; Chumming et al., 2017; Heiligeburg et al., 2012; Molley-Copson, Jents, & Swartz, 2014; Papas & Hamlis, 2011; Prestage et al., 2008; Smit & et al., 2015; Stoddard, 2017)

- Association with facilitation HIV: (Boschel et al., 2005; Macmillan et al., 2007; Pankey et al., 2007; Prestage et al., 2009; Grover et al., 2008)


- Potential risk of serious overdose and death (Hooker et al., 2017; Caldwell, Chow, Burns, Folkins, & Byrd, 2004; Licch & Kupferschmidt, 2004)

- Drug-drug interactions (Plowin, 2016; Bracho, 2015)
Questions for Consideration

• How extensively does substance use contribute to new infections? Prevent patients from seeking medical care? Affect retention in care?
• Is the problem growing?
• How can it be best managed in the individual and in the community?
Drug abuse in HIV infected patients.

Chem-sex role

Perelló R.
Servei d’Urgències. Hospital Clínic de Barcelona.

Cerebrospinal Fluid EBV Replication is Associated with Compartmental Inflammation and Pleocytosis in HIV-positive naïve and Treated Individuals


Tommaso Lupia
University of Torino
Clinic of Infectious Diseases
Ospedale Amedeo di Savoia

Cerebrospinal Fluid HIV-RNA and Neurocognitive Deficits:
Are Lumbar Punctures Needed in Impaired Subjects with Undetectable Plasma Viral Load?


Unit of Infectious Diseases,
Department of Medical Sciences,
University of Torino, Torino
Hot topics on CNS and HIV
(most relevant presentations in conferences or articles published recently)

Paola Cinque
Department of Infectious Diseases
San Raffaele Hospital, Milan, Italy
Compartmentalization and Clonal Amplification of HIV-1 Variants in CSF during Primary Infection
Shnell G. et al., J Virol 2010

Discordance = compartmentalization

CSF
plasma

Poster # 364
CSF HIV-1 compartmentalization by env deep sequencing: relation to neuronal injury
University of California, San Francisco, California, University of California, Oxford, University of North Carolina Chapel Hill, Yale University, New Haven, Connecticut.

1. Neurosympotomatic (NA) CD4 >200 cells/μl (N=8)
2. NA CD4 <200 with normal CSF NFL (NFL-negative) (N=8)
3. NA CD4 <200 with elevated NFL (NFL+)(N=10)
4. HAV (N=7), all with elevated CSF NFL

- Major (>30%) CSF env sequence compartmentalization in all of the 7 HAD subjects
- CSF env sequence compartmentalization also present in the other groups, including the two without evidence of ongoing CNS injury (normal CSF NFL)
- CSF HIV-1 compartmentalization does not provide a simple biomarker of neuropathic infection
Early ART is Associated with lower HIV DNA Molecular Diversity and lower Inflammation in CSF but Does Not Prevent the Establishment of Compartmentalized HIV DNA Populations (Oliveira MF, PLOS Pathogens 2017)
Sequential paired blood and CSF from 16 ART-treated suppressed pts (after a median of 2.6 years from ART start):
- 9 early ART (<4 months of infection)
- 7 late ART (>14 months after infection)

Early ART was associated with lower molecular diversity of HIV DNA in CSF in comparison to late ART
Latency reversing agents (LRA)

- Histone deacetylase inhibitors (HDACi, e.g., varinostat)
- Bromodomain inhibitors
- Protein kinase C agonists
- Cytokines, such as IL-2 and IL-15
- Others...

Reactivation of SIV reservoirs in the brain of virally suppressed macaques following administration of latency reversing agents (Gama L et al., AIDS 2017)

- 3 SIV-infected pigtailed macaques ART-treated since 12 days p.i.
- Macaque Mn0 (red) control
- Macaques Mn1 (blue) and Mn2 (green) treated with ingenol-B starting at 530 days p.i. with ingenol-B and ingenol-B plus varinostat

CNS-specific regulatory elements in brain-derived HIV-1 strains affect responses to latency-reversing agents with implications for cure strategies (LR Grey, Molecular Psychiatry, 2016)

CNS-derived HIV-1 strains (grey) have LTR polymorphisms within and surrounding the Sp transcription factor motifs

LTR polymorphisms result in decreased binding to Sp1 and reduced transcriptional activity of CNS-derived HIV (orange) compared with lymphoid-derived LTRs (blue)
Questions for Consideration

- What standardized methods should be used to ensure comparability between trials?
  - Neuropsychological testing, NSS, imaging, biomarkers
  - How often should participants be assessed?
  - For how long should participants be followed?
- The Frascati guidelines are a decade old. Should they be updated considering 10 years of progress?
- What are the most promising interventions now?
  - Changing “habits”: Exercise, diet
  - Treating comorbid disease: depression, substance use, sleep disorders, metabolic and vascular disease
  - Adjunctive therapies: rivastigmine, paroxetine

Questions for Consideration

- Do current ART regimens have sufficient potency outside and inside the CNS to minimize the effects of HIV replication?
  - Will we continue to see CSF viral escape?
- How will the clinical environment shift over the next 5 years (long-acting ART, new classes of drugs)?
- How will we control inflammation from low-level replication and production of neurotoxic HIV proteins?
- How do we implement neurotoxicity data into the clinic?
- Will we need different treatment strategies for patients with different characteristics (e.g., aged)?

Questions for Consideration

- Do neuropsychiatric adverse events occur with both dolutegravir and elvitegravir?
  - Will bictegravir also have neuropsychiatric side effects?
  - Is raltegravir an attractive alternative for initial therapy for patients with risk factors or for switching when AEs occur?
- What is the contribution of other risk factors (e.g., abacavir, age, sex)?
- If symptoms subside but drug is continued, will cumulative injury occur with resulting long-term cognitive or mood disorders?
  - If they do, will they be reversible?

Questions for Consideration

- How extensively does substance use contribute to new infections? Prevent patients from seeking medical care? Affect retention in care?
- Is the problem growing?
- How can it be best managed in the individual and in the community?
Happy Birthday!

International Symposium on Neuropsychiatry & HIV

10th

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