Treating CNS HIV Infection and Disease

Why, How and When?

Richard W. Price, M.D.
Department of Neurology, UCSF/SFGH

Preface: Reasons for Renewed Interest in Treatment of CNS HIV

- Continued CNS infection/disease in treated patients
- Limited CNS access and efficacy of individual drugs and combinations
- Potential additive/synergistic HIV neuropathogenic effects combined with
  - Prolonged survival
  - Brain aging
- Potential impediment to eradication
- CNS drug toxicity

Outline: Treatment of CNS HIV

- Why? Background
  - Untreated CNS HIV infection and disease
  - Effects of ART on CNS infection and disease
  - Continued neurological impairment
- How? Drug properties and uses
  - CNS drug access and effectiveness
- When? Practical clinical application
  - Evaluation approaches
  - Untreated patients
  - Treated patients

Untreated CNS/CSF Infection

- CNS/CSF infection is a nearly ubiquitous facet of systemic infection
  - Early entry of CNS during primary infection
  - Continues through course of untreated infection
  - Dynamically linked to systemic viremia
- Evolution of CSF infection types
  - Early, meningitic: Non-compartmentalized (transitory, CD4High)
  - Late, encephalitic: Compartmentalized (autonomous)
    - T-tropic (CD4High)
    - M-tropic (CD4Low)
- Driver of local immune activation and neural injury
Plasma & CSF HIV RNA & CSF WBCs in Untreated Subjects across the Spectrum of CD4

113 Untreated HIV+ (8 ADC)
- CSF HIV detection common across CD4 range
- Variable relationship of CSF to plasma VL
- CSF pleocytosis common across CD4 range
- ADC findings cluster with non-ADC

Neuro-Asymptomatic: Non-compartmentalized T-tropic

- Neurosymptomatic subjects
- Genetic mixing of CSF and plasma populations
- Minor CSF isolation

ADC: Compartmentalized, M-tropic

- ADC patients
- Strong CSF compartmentalization
- Independent evolution-amplification of CSF HIV

Unchecked HIV Encephalitis and ADC (HAD)

- Pathological substrate
  - HIV encephalitis (HIVE)
  - Multinucleated giant cell encephalitis
  - White matter pallor
  - Micro-neuronal abnormalities
  - Vacuolar myelopathy
- Cell site of HIV replication
- Compartmentalized
- Pathways to brain injury
  - Viral gene products: signal and toxic
  - Cell (MΦ) gene products: endogenous toxins
  - Glutamate receptor ligands
Effect of cART on CNS HIV Infection

• Common viral suppression
• Uncommon CNS escape
  • Symptomatic
  • Asymptomatic
• Residual replication?
  • Level of CSF HIV in well-treated patients
  • Continued CNS injury?

CSF HIV Responses to Treatment: Older Experience

- Offs – 67 off ART for >3 months
- Failures – 48 on ART, plasma VL > 50 cpm
- Successes – 33 on ART, plasma VL < 50

CSF HIV Responses to Treatment: Older Experience

A. Off Treatment
B. ‘Failed’ Treatment
C. ‘Successful’ Treatment

- Systemic ‘success’ usually associated with CSF suppression
- In ‘failed’ treatment, CSF HIV RNA relatively lower than plasma
- CSF HIV assumes different relation to plasma HIV
- Hence, treatment usually favorably impacts CSF HIV infection

Exceptions to Successful CNS Treatment: CSF Escape

  - CSF escape (or dissociation) clearly indicative of active CNS disease
  - CSF escape of uncertain pathogenetic significance

Symptomatic CSF Escape: Canestri et al

• Retrospective case series patients with neurological symptoms and HIV in CSF with suppressed plasma
  - CSF > 200 cpm, plasma < 50 cpm or CSF > 10s plasma in treated patients
  - 2 centers, 6000 patients/year
  - Review over 5 year period
• 11 patients
  - Acute or subacute neurological disease
  - 10/11 CSF pleocytosis
  - Median CSF HIV 880 cpm (588 – 12,885)
  - Resistance mutations in 7/8
  - All improved after optimization of treatment with respect to:
    • Resistance
    • CPE

Symptomatic CSF Escape

- Presented with predominantly 'myelopathic' ADC, in March 2000
- Plasma VL 378 & CSF 5,467
- On ddI/SGC/RTV - switched to ABC/NVP/IDV/RTV

Symptomatic Viral 'Dissociation' in Treated Patient

- Presented with predominantly 'myelopathic' ADC, in March 2000
- Plasma VL 378 & CSF 5,467
- On ddI/SGC/RTV - switched to ABC/NVP/IDV/RTV

Asymptomatic CSF Escape: Eden et al

- Retroactive case series of patients on contemporary therapies with:
  - HIV in CSF (>50 cpm) with suppressed (<50 cpm) plasma
  - 69 total subjects
    - 7 with detectable CSF (10%)
    - Median CSF HIV 121 cpm (54 – 213)
    - CSF pleocytosis: no different from non-escape
    - Resistance mutations not done
    - No relation to cpe score

Asymptomatic CSF Escape with Contemporary Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CN-escape</th>
<th>CN non-escape</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>median (range)</td>
<td>56 (36-64)</td>
<td>41 (22-71)</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>42 (73%)</td>
<td>45 (73%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>CSF and blood, HIV RNA (CD4+ T cells)</td>
<td>median (CPM)</td>
<td>230 (490-822)</td>
<td>525 (350-642)</td>
</tr>
<tr>
<td>CSF load: HIV RNA (logs)</td>
<td>median (logs)</td>
<td>1.09 (1.06-1.74)</td>
<td>1.09 (1.06-1.74)</td>
</tr>
<tr>
<td>CSF cell count</td>
<td>median (103)</td>
<td>1.4 (1-8.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSF cell type</td>
<td>median (103)</td>
<td>1.4 (1-10.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>CSF HIV-1 viral load (103)</td>
<td>median (103)</td>
<td>7.3 (4-7.9)</td>
<td>7.4 (4.8-9.1)</td>
</tr>
<tr>
<td>CD4 count (103)</td>
<td>median (103)</td>
<td>7.3 (1.5-8.1)</td>
<td>7.1 (4.8-9.1)</td>
</tr>
<tr>
<td>WBC, c/µL</td>
<td>median (103)</td>
<td>4.1 (1-6.4)</td>
<td>1.9 (1.3-8.6)</td>
</tr>
<tr>
<td>Platelet count, c/µL</td>
<td>median (103)</td>
<td>174 (52-392)</td>
<td>214 (127-542)</td>
</tr>
</tbody>
</table>
Antiretroviral Drugs of CSF Viral Escape Subjects

<table>
<thead>
<tr>
<th>Drug</th>
<th>CSF viral escape, no. (%)</th>
<th>Total, no. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elv</td>
<td>4 (15)</td>
<td>27</td>
</tr>
<tr>
<td>Lpvh</td>
<td>1 (3)</td>
<td>21</td>
</tr>
<tr>
<td>AtvE</td>
<td>2 (10)</td>
<td>21</td>
</tr>
<tr>
<td>Tat</td>
<td>3 (9)</td>
<td>34</td>
</tr>
<tr>
<td>Abc</td>
<td>4 (22)</td>
<td>18</td>
</tr>
<tr>
<td>Zidv</td>
<td>0 (0)</td>
<td>17</td>
</tr>
<tr>
<td>3TC</td>
<td>4 (10)</td>
<td>43</td>
</tr>
<tr>
<td>FTC</td>
<td>3 (12)</td>
<td>26</td>
</tr>
</tbody>
</table>

**NOTE:** STC, lamivudine; Abc, abacavir; Atv, atazanavir; Elv, efavirenz; FTC, emtricitabine; Lpvh, lopinavir/ritonavir; Tat, tenofovir; Zid, zidovudine.

A Case of CSF Escape: Confounded Symptoms

- Day 2053: Genotyping - K65R, no NNRT or PI resistance
- From CPE2010 of 13 to 7

Very Low Residual CSF HIV RNA in Suppressed Subjects in Intensification Study

HIV-Related CNS Disease: Nomenclature

- Early: clinical phenotypic diagnosis & classification by functional criteria
  - ADC (MSK) staging
- Present: 'Frascati' diagnosis & classification based on neuropsychological testing impairment: HAND (HIV-associated neurocognitive disorders)
  - HAD: HIV-associated dementia (2 domains >2SD below mean)
  - NMD: mild neurocognitive disorder (2 domains >1SD below mean and symptoms or functional impairment)
  - ANI: asymptomatic neurocognitive impairment (2 domains >1SD below mean without symptoms)
Impact of Treatment on Severe CNS Disease over 3 Epochs in a Danish Nationwide Cohort

- Study design:
  - Nationwide, population-based cohort study using Danish registries
  - Severe neurocognitive disorders (SNCD)
  - Incidence of and survival after SNCD in HIV-infected patients, compared with a general population control cohort

- Findings:
  - 32 cases per 4,452 HIV+
  - 120 cases per 62,328 controls
  - Relative risk 10.1 when CD4 <350 (optimal CD4 >500)
  - Relative incidence in HIV+ approached HIV- in 2005-2008
  - Mortality higher in HIV+ SNCD


Continued CNS Disease in Treated: Prevalence of Neuropsychological Impairment

- Study of 200 subjects with treatment-induced plasma viral suppression
  - 27% Cognitive complaints
  - 50 with neurological complaints (64% impairment)
  - 24% asymptomatic neurocognitive impairment (ANI)
  - 52% mild neurocognitive disorder (MND)
  - 8% HAD
  - 50 without neurological complaints (64% impairment)
    - 60% ANI
    - 5% HAD


Targeting the CNS: Drug Access and Effect

- Evaluating systemic therapy
- Evaluating CNS drug effects
- Comparing systemic and CNS effects

Hierarchy of Drug Properties in Treating Systemic HIV Infection

- Systemic anti-HIV potency/efficacy
- Low toxicity and side effect profile
- Favorable drug-drug interactions
- Convenient dose schedule (favoring adherence)
- CNS treatment effectiveness
- Low cost

Local Treatment of CNS Infection: Drug CNS ‘Penetration’ and Effectiveness

- CNS PK
  - CSF commonly used as brain PK surrogate
- CNS PD
  - Very limited data on most drugs
- Practical guide
  - CNS Penetration Effectiveness (CPE) Scoring (Letendre and colleagues)
    - 2008
    - 2010

CNS Penetration Effectiveness (CPE) 1:
Original 2008, Modified 2010

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>1</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Enfuvirtide</td>
<td>Didanosine</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Lamivudine</td>
<td>Stavudine</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td>Zalcitabine</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNRTIs</th>
<th>1</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine</td>
<td>Nevirapine</td>
<td>Efavirenz</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PIs</th>
<th>1</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>Saquinavir</td>
<td>Indinavir</td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaletra</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Integrase Inhibitors

<table>
<thead>
<tr>
<th>RTV Inhibitors</th>
<th>1</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc</td>
<td>Raltegravir</td>
<td>Elvitegravir</td>
<td></td>
</tr>
</tbody>
</table>

CNS Penetration Effectiveness (CPE) 2:
Original 2008, Modified 2010

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>1</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Enfuvirtide</td>
<td>Didanosine</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Lamivudine</td>
<td>Stavudine</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td>Zalcitabine</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNRTIs</th>
<th>1</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine</td>
<td>Nevirapine</td>
<td>Efavirenz</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PIs</th>
<th>1</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>Saquinavir</td>
<td>Indinavir</td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaletra</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Integrase Inhibitors

<table>
<thead>
<tr>
<th>RTV Inhibitors</th>
<th>1</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc</td>
<td>Raltegravir</td>
<td>Elvitegravir</td>
<td></td>
</tr>
</tbody>
</table>

CNS Penetration Effectiveness (CPE) 3:
Original 2008, Modified 2010

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>1</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Enfuvirtide</td>
<td>Didanosine</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Lamivudine</td>
<td>Stavudine</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td></td>
<td>Zalcitabine</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNRTIs</th>
<th>1</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine</td>
<td>Nevirapine</td>
<td>Efavirenz</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PIs</th>
<th>1</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>Saquinavir</td>
<td>Indinavir</td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaletra</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Integrase Inhibitors

<table>
<thead>
<tr>
<th>RTV Inhibitors</th>
<th>1</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc</td>
<td>Raltegravir</td>
<td>Elvitegravir</td>
<td></td>
</tr>
</tbody>
</table>
CNS Penetration Effectiveness (CPE) 2: 2010

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>Abacavir</th>
<th>Lamivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNRTIs</th>
<th>Nevirapine</th>
<th>Darunavir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PIs</th>
<th>Darunavir</th>
<th>Atazanavir</th>
<th>Nelfinavir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry inhibitors</th>
<th>Maraviroc</th>
<th>Enfuvirtide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Integrase inhibitors</th>
<th>Raltegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Initial Systemic Treatment Preferences & CNS Effects: Conflicting Priorities

**Conflict between systemic and CNS treatment optimization!**

Why Do Common Regimens Work So Well?

- **Systemic Effects**
  - Reduce CNS viral reseeding
  - Reduce immune activation
  - Reduce traffic of activated target cells
  - Enhance immune control?

- **CNS Effects**
  - Underestimated by CPE score
  - CSF is not equivalent to brain
  - Intracellular concentrations and effects paramount for most
  - Older regimens more effective?
Evaluating Patients for CNS Treatment: Clinical

- **Screen**
  - Bedside screen
  - Quantitative screen
- **Evaluation**
  - Neurological consultation
  - Formal quantitative (neuropsychological) testing

Evaluating Patients for CNS Treatment: Laboratory

- **Neuroimaging (MRI)**
  - Alternative diagnoses
  - HIV-effects
- **CSF examination**
  - Alternative diagnoses
  - HIV infection
    - HIV RNA
    - Drug susceptibility
  - Inflammation
  - Neural injury

Off-Treatment Algorithm

```
Off Therapy
/\                         /
|                           |
Bedside Screening          QNP Screening
/\                         /
|                           |
Normal CNS Function         Standard ART
/\                         /
| yes                       |
| usually                  |
| consider                 |
| Severe CNS Dysfunction    |
| Ahl Do?                  |
| no                       |
| More Neuro-Effective ART |
```

On-Treatment Algorithm

```
On Therapy
/\                         /
|                           |
Bedside Screening          QNP Screening
/\                         /
|                           |
Normal CNS Function         Continue Standard ART
/\                         /
| yes                       |
| reset                    |
| Progressive              |
| Severe CNS Dysfunction    |
| Ahl Do?                  |
| no                       |
| CSF Escape               |
| yes                      |
| More Neuro-Effective ART |
```
Steps in Approach to HIV-Related Neurological Disease

1. Suspect Clinically
2. Diagnose Biologically
3. Treat Virologically

CNS Brain Infection and Disease: Some Conclusions

- cART has been very effective in reducing severe HIV-related brain injury
- But CNS impairment continues
  - May reflect past injury
    - Supported by relation to CD4 nadir
    - Should decrease with earlier treatment initiation
  - Frequency/intensity of ongoing (active) injury uncertain
  - Exceptions are cases with symptomatic CSF escape
  - Significance of asymptomatic CSF HIV or immune activation uncertain
- Targeting CNS infection and disease remains to be refined with respect to:
  - Settings
  - Choices of treatment

Acknowledgements

- Clinical/CSF
  - Magnus Gisslen
  - Lars Hagberg
  - Arvid Eden
  - Aylin Yilmaz
  - Serena Spudich
  - Paola Cinque
  - Evelyn Lee
  - Julia Peterson

- Immunology
  - Dietmar Fuchs
  - Elizabeth Sinclair

- Neural Biomarkers
  - Henrik Zetterberg
  - Ulf Andreasson
  - Jan Krut
  - Lars Rosengren

- Virology
  - Teri Liegler
  - Gretja Schnell
  - Ron Swanstrom
  - Sarah Palmer
  - Victor Dahl

RWP Potential Conflicts: Investigator-initiated research grant Merck & Co; Honorarium Abbott