Clinical notes:
Management of HAART in patients with HAND

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

11 Residential Course on Clinical Pharmacology of Antiretrovirals
Turin, 20-22 January 2016
The CNS and ART: features that distinguish CNS from systemic infection

- Infection of CNS macrophages (macrophage as cell “compartment”)

- Presence of the brain barriers (CNS as anatomical “compartment”)

CNS compartmentalization of HIV infection

No CSF compartmentalization (neuroasymptomatic)

CSF compartmentalization (ADC)

Pillai SK et al., Brain 2006
Concept of CNS-targeted ART

No CSF compartmentalization

ART effective systemically is also effective intrathecally

CSF compartmentalization

ART effective systemically is **not necessarily** also effective intrathecally

ARV drugs should be able:
1. To cross the CNS barriers
2. To inhibit HIV replication in CNS macrophages
The effect of HIV in the CNS in 2016 (HAND: HIV-associated neurological disorders)

• In untreated patients
  – HIV-associated dementia
  – Mild neurocognitive/motor impairment

• In treated patients
  – Neurocognitive impairment
  – CSF viral escape
The effect of HIV in the CNS in 2016 (HAND: HIV-associated neurological disorders)

• In untreated patients
  – HIV-associated dementia
  – Mild neurocognitive/motor impairment

→ May occur in ‘AIDS presenters’
→ Is there an indication for a CNS-targeted ART?
Different short-term kinetics of virological response in CSF and plasma of ART-treated patients

Parallel CSF/plasma response

- CSF
- Plasma

Slower CSF response

- CD4<sub>0</sub> 267
- WBC<sub>0</sub> 33

- CD4<sub>0</sub> 59
- WBC<sub>0</sub> 66

- CD4<sub>0</sub> 77
- WBC<sub>0</sub> 46

- CD4<sub>0</sub> 3
- WBC<sub>0</sub> 0

Staprans et al., AIDS 1999
Kinetics of virological response in CSF and plasma in a patient with ADC

ART: 3TC+d4T+IDV

HIV-1 RNA copy numbers / mL

Months of therapy

0  3  6  9  12  15

184V

WT

CSF

plasma
Kinetics of virological response in CSF and plasma in a patient with ADC

ART: 3TC+d4T+IDV

HIV-1 RNA copy numbers / mL

Months of therapy

184V

WT
Kinetics of virological response in CSF and plasma in a patient with ADC

ART: 3TC+d4T+IDV

HIV-1 RNA copy numbers / mL

Months of therapy

CSF
plasma

184V
WT

184V

184V

0 3 6 9 12 15
Kinetics of virological response in CSF and plasma in a patient with ADC

ART: 3TC+d4T+IDV

HIV-1 RNA copy numbers / mL

Months of therapy

CSF
plasma

WT
184V
184V
184V
Randomized Clinical Trial of Antiretroviral Therapy for Prevention of HAND in naïve pts (Beijing)

NVP+AZT+3TC vs. EFV+TDF+3TC

- 1036 pts, no NCI
- 97-100% M, median CD4 235-222/µL, median logVL 4.2 c/mL
- 8 test battery

Scott Letendre et al., CROI 2015
NC Function in Africans Failing First-Line ART and Responses to Second Line (EARNEST, Uganda)

- 1036 pts
- 58% F, median CD4 71/µL, VL>100,000 42%
- NPZ3 (Trail Making 1-2, Grooved Pegboard)

**PI+2-3 NRTIs vs. PI+RAL vs. PI mono**

BL Z-score: -2.96

Andrew D. Kambugu, CROI 2015
The direct effect of HIV in the CNS (HAND: HIV-associated neurological disorders)

- In untreated patients
  - HIV-associated dementia
  - Mild neurocognitive/motor impairment

Is there an indication for a CNS-targeted ART?

→ May be useful to accelerate CSF clearance in early phase
→ Longer-term effect on NC function not established
The direct effect of HIV in the CNS (HAND: HIV-associated neurological disorders)

- In treated patients
  - Neurocognitive impairment
  - CSF viral escape

→ Is there the indication for a CNS-targeted ART?
Prevalence of HAND - Rome, 2009-2014

ANI: Asymptomatic Neurocognitive Impairment (NP test abnormalities only)
MND: Mild Neurocognitive Disorder (NP test abn + mild functional problems)
HAD: HIV-associated dementia

83% suppressed plasma VL
Potential causes of cognitive deterioration: what mechanisms?

- HIV (HIV-associated NCI)
- Previously established irreversible tissue damage by HIV or other causes (legacy effect)
- Aging
- Psychiatric disorders
- Drugs, alcohol
- Alzheimer’s and other neurodegenerative diseases
- Metabolic problems and cerebro-vascular disease
- Drug toxicity (ART, other drugs)?
### NCI and ART neuropenetration

<table>
<thead>
<tr>
<th>Study</th>
<th>Cysique</th>
<th>Tozzi</th>
<th>Smurzynski</th>
<th>Marra</th>
<th>Winston</th>
<th>Arendt</th>
<th>Garvey</th>
<th>Rourke</th>
<th>Ciccarelli</th>
<th>Robertson</th>
<th>Kahouadj</th>
<th>Ellis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>UCSD CIT</td>
<td>INMI</td>
<td>ALLRT</td>
<td>ACTG 736</td>
<td>ALTAIR</td>
<td>Dusseldorf NA Cohort</td>
<td>Imperial College, UK</td>
<td>OHTN Cohort Study</td>
<td>UCSC</td>
<td>ACTG 5199</td>
<td>INSERM</td>
<td>HNRP/UCSD</td>
</tr>
<tr>
<td>37</td>
<td>185</td>
<td>2,636</td>
<td>26</td>
<td>30</td>
<td>3,883</td>
<td>101</td>
<td>545</td>
<td>101</td>
<td>860</td>
<td>54</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>CPE: CSF VL</td>
<td>Lower VL</td>
<td>No CSF</td>
<td>No CSF</td>
<td>Lower VL</td>
<td>No CSF</td>
<td>Lower VL</td>
<td>No CSF</td>
<td>No CSF</td>
<td>No CSF</td>
<td>No CSF</td>
<td>No CSF</td>
<td>No effect</td>
</tr>
<tr>
<td>Number of NP Tests</td>
<td>6</td>
<td>15</td>
<td>3</td>
<td>4</td>
<td>CogState</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>18</td>
<td>6</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>CPE: NP Tests</td>
<td>Better</td>
<td>Better</td>
<td>Better (only by &gt;3 drugs)</td>
<td>Poorer</td>
<td>Poorer</td>
<td>Better</td>
<td>No effects</td>
<td>Not conclusive</td>
<td>Better</td>
<td>No effect</td>
<td>Poorer</td>
<td>No effect</td>
</tr>
<tr>
<td>Prospective</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Controlled</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Norms for NP Change</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>


(Courtesy of S. Letendre)
The direct effect of HIV in the CNS (HAND: HIV-associated neurological disorders)

- In treated patients
  - Neurocognitive impairment

Is there the indication for a CNS-targeted ART?

→ Effect on NC function not established
CSF viral escape

CSF VL > 50 c/mL (if plasma VL suppressed) or CSF VL > 0.5 -1 log plasma VL (if plasma VL > 50)

Asymptomatic or symptomatic

Neuro-symptomatic CSF viral escape (dementia)

- M, 50
- 2008: Progressive dementia

- History of HIV-D
  - CD4 nadir: 145
  - 1991: Starts ART
  - Since 2005 TDF, FTC, LPV/r

- CD4 632
- Plasma HIV 265 c/mL
- CSF HIV 750 c/mL
- CSF cells 26/µL

→ CSF and plasma mutations to NRTIs (67, 75, 77, 118, 184, 210, 215, 219) and PIs (46, 54, 82, 90)
Neuro-symptomatic CSF viral escape (dementia)

- M, 50
- 2008: Progressive dementia

- History of HIV-D
- CD4 nadir: 145
- 1991: Starts ART
- Since 2005 TDF, FTC, LPV/r

- CD4 632
- Plasma HIV 265 c/mL
- CSF HIV 750 c/mL
- CSF cells 26/µL

→ CSF and plasma mutations to NRTIs (67, 75, 77, 118, 184, 210, 215, 219) and PIs (46, 54, 82, 90)

→ Resolution by cART optimization for genotypic profile
Neuro-symptomatic CSF viral escape (meningoencephalitis)

- M, 26
- **2010**: Headache, disartrhia, ataxia (days)

- History of systemic OIs
- CD4 nadir: 9
- 2009: Starts ART (AZT,3TC,LPV/r)
- Change to **TDF, FTC, ATV**

- CD4 290
- **Plasma HIV 98 c/mL**
- **CSF HIV 5200 c/mL**
- **CSF cells: 200/µL**

No CSF mutations to NRTIs and PIs
Neuro-symptomatic CSF viral escape (meningoencephalitis)

- M, 26
- **2010**: Headache, disarthria, ataxia (days)
- History of systemic OIs
- CD4 nadir: 9
- 2009: Starts ART (AZT,3TC,LPV/r)
- Change to **TDF, FTC, ATV**

- CD4 290
- Plasma HIV 98 c/mL
- CSF HIV 5200 c/mL
- CSF cells: 200/µL

No CSF mutations to NRTIs and PIs

→ Resolution by cART optimization for neuropenetration
Neuro-symptomatic CSF viral escape

- Can present with NCI and dementia or focal CNS disease
- Chronic progressive or acute presentation
- In patients with/out a history of dementia
- Low nadir CD4
- With/out ART resistance
Relapse of CSF escape upon ART switch for toxicity or simplification

<table>
<thead>
<tr>
<th>Pt</th>
<th>ART at CSF escape</th>
<th>duration (months)</th>
<th>Pla VL</th>
<th>CSF VL</th>
<th>Effective ART after CSF escape</th>
<th>Pla VL</th>
<th>CSF VL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3TC, ABV, FPV/r</td>
<td>30</td>
<td>&lt;50</td>
<td>93</td>
<td>AZT, 3TC, ABV, FPV/r</td>
<td>&lt;50</td>
<td>&lt;50</td>
</tr>
<tr>
<td></td>
<td>TDF, FTC, ATV</td>
<td>24</td>
<td>98</td>
<td>5200</td>
<td>AZT, 3TC, DRV/r (bid)</td>
<td>&lt;50</td>
<td>&lt;50</td>
</tr>
<tr>
<td>2</td>
<td>TDF, FTC, FPV/r</td>
<td>24</td>
<td>4067</td>
<td>75000</td>
<td>3TC, ABV, LPV/r</td>
<td>&lt;50</td>
<td>&lt;50</td>
</tr>
<tr>
<td>3</td>
<td>TDF, FTC, DRV/r (qd)</td>
<td>60</td>
<td>&lt;1</td>
<td>837*</td>
<td>AZT, 3TC, RAL, DRV/r (bid)</td>
<td>&lt;1</td>
<td>&lt;50</td>
</tr>
<tr>
<td>4</td>
<td>TDF, FTC, DRV/r (qd)</td>
<td>60</td>
<td>&lt;1</td>
<td>853*</td>
<td>AZT, 3TC, RAL, DRV/r (bid)</td>
<td>&lt;1</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

* presence of drug resistance mutations
Relapse of CSF escape upon ART switch for toxicity or simplification

<table>
<thead>
<tr>
<th>Pt</th>
<th>ART at CSF escape</th>
<th>duration (months)</th>
<th>Pla VL</th>
<th>CSF VL</th>
<th>Effective ART after CSF escape</th>
<th>Pla VL</th>
<th>CSF VL</th>
<th>ART switch (2nd CSF escape)</th>
<th>duration (months)</th>
<th>Pla VL</th>
<th>CSF VL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3TC, ABV, FPV/r</td>
<td>30</td>
<td>&lt;50</td>
<td>93</td>
<td>AZT, 3TC, ABV, FPV/r</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>AZT, 3TC, ABV, FPV/r</td>
<td>12</td>
<td>&lt;40</td>
<td>549</td>
</tr>
<tr>
<td>2</td>
<td>TDF, FTC, ATV</td>
<td>24</td>
<td>98</td>
<td>5200</td>
<td>AZT, 3TC, DRV/r (bid)</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>AZT, 3TC, DRV/r (bid)</td>
<td>42</td>
<td>&lt;40</td>
<td>1596</td>
</tr>
<tr>
<td>3</td>
<td>TDF, FTC, FPV/r</td>
<td>24</td>
<td>4067</td>
<td>75000</td>
<td>3TC, ABV, LPV/r</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>3TC, ABV, LPV/r</td>
<td>42</td>
<td>205</td>
<td>3439*</td>
</tr>
<tr>
<td>4</td>
<td>TDF, FTC, DRV/r (qd)</td>
<td>60</td>
<td>&lt;1</td>
<td>837*</td>
<td>AZT, 3TC, RAL, DRV/r (bid)</td>
<td>&lt;1</td>
<td>&lt;50</td>
<td>AZT, RAL, ABV, DRV/r (bid)</td>
<td>10</td>
<td>&lt;1</td>
<td>853*</td>
</tr>
</tbody>
</table>

* presence of drug resistance mutations
### Relapse of CSF escape upon ART switch for toxicity or simplification

<table>
<thead>
<tr>
<th>Pt</th>
<th>ART at CSF escape*</th>
<th>duration (months)</th>
<th>Pla VL</th>
<th>CSF VL</th>
<th>Effective ART after CSF escape*</th>
<th>Pla VL</th>
<th>CSF VL</th>
<th>ART switch (2nd CSF escape)*</th>
<th>duration (months)</th>
<th>Pla VL</th>
<th>CSF VL</th>
<th>Effective ART after 2nd CSF escape*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3TC, ABV, FPV/r</td>
<td>30</td>
<td>&lt;50</td>
<td>93</td>
<td>AZT, 3TC, ABV, FPV/r</td>
<td>&lt;50</td>
<td>n.d.</td>
<td>AZT, 3TC, ABV, FPV/r</td>
<td>5</td>
<td>&lt;40</td>
<td>549</td>
<td>AZT, 3TC, ABC, FPV/r</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3TC, ABV, DRV/r (bid)</td>
<td></td>
<td></td>
<td>AZT, ABV, 3TC, DRV/r (bid)</td>
<td></td>
<td></td>
<td></td>
<td>AZT, 3TC, DRV/r (bid), RAL</td>
</tr>
<tr>
<td>2</td>
<td>TDF, FTC, ATV</td>
<td>24</td>
<td>98</td>
<td>5200</td>
<td></td>
<td>&lt;1</td>
<td>&lt;1</td>
<td></td>
<td>5</td>
<td>&lt;40</td>
<td>1596</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>TDF, FTC, FPV/r</td>
<td>24</td>
<td>4067</td>
<td>75000</td>
<td>AZT, 3TC, ABV, LPV/r</td>
<td>&lt;50</td>
<td>n.d.</td>
<td>AZT, 3TC, LPV/r, TDF, FTC, NVP</td>
<td>32</td>
<td>205</td>
<td>3439*</td>
<td>AZT, 3TC, DRV/r (bid)</td>
</tr>
<tr>
<td>4</td>
<td>TDF, FTC, DRV/r (qd)</td>
<td>60</td>
<td>&lt;1</td>
<td>837*</td>
<td>AZT, 3TC, RAL, DRV/r (bid)</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>AZT, RAL, ABV, 3TC, DRV/r (bid)</td>
<td>2</td>
<td>&lt;1</td>
<td>853*</td>
<td>AZT, 3TC, DRV/r (bid), DTG</td>
</tr>
</tbody>
</table>

* All responded clinically

* presence of drug resistance mutations
Possible risk factors in CSF escape

• Size of brain ‘reservoir’
• Resistance
• Adherence
• Efficacy of individual drugs/regimens
  – CNS ‘penetration’
  – Efficacy in macrophages/microglial cells
The Strategic Timing of Anti-Retroviral Treatment (START)
Neurology Substudy: Study Design

HIV-infected individuals, ART-naïve, CD4+ count >500 cells/µL, No prior AIDS

START Study Randomization
N=4658 START participants
Neurology Substudy N=608 participants

Immediate ART
(following randomization)
N=297 randomized
N=291 with follow-up data

Deferred ART
CD4+ < 350 cells/µL or AIDS
N=311 randomized
N=301 with follow-up data

- Planned sample size: N=600, 4 years of follow-up
- For this analysis, follow-up was censored on May 26, 2015 (unblinding of the START study), mean follow-up 3.3 years.

(Price RW et al., EACS Barcelona 2015)
Primary Outcome: Change in QNPZ-8 from baseline

- QNPZ-8 increased in both treatment groups
- Estimated difference Imm. – Def. groups:
  -0.01 (95% CI: -0.06 to 0.03)
  \[ P=0.63 \]

Statistical Methods:
*Comparison by intent-to-treat, longitudinal mixed model, adjusted for baseline QNPZ-8 and study visit.*

(Price RW et al., EACS Barcelona 2015)
START Study: Conclusions

• No overall neurocognitive advantage (or disadvantage) for immediate ART initiation in asymptomatic treatment-naïve individuals with high CD4 counts
  - Suggests: low prevalence of ART-reversible neurocognitive impairment
  - Suggests: low incidence of ART-preventable neurocognitive decline over period of study off treatment
  - No clear evidence of neurotoxicity

(Price RW et al., EACS Barcelona 2015)
CNS targeted-ART is indicated:

- Untreated patients
  → HIV encephalitis, to accelerate HIV clearance (?)

- Treated patients
  → CSF viral escape, to suppress ongoing CNS replication
Grazie

Neurovirology Unit and colleagues at San Raffaele Scientific Institute: Francesca Ferretti, Laura Passeri, Daniele Mennonna, Ester Tuveri, Valentina De Zan e Francesco Campanelli, Simonetta Gerevini, Adriano Lazzarin

Collaborators and inspirators: Dick Price (UCSF); Magnus Gisslen and Lars Hagberg (Univ. of Goteborg); Serena Spudich (Yale Univ.)

Guidelines companions: Andrea Antinori, Andrea Calcagno (Italian Guidelines); Alan Winston, Renaud De Pasquier (EACS Guidelines)

Funding: