Central Nervous System (CNS) Escape in HIV

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CNS Escape

Loss of control of brain HIV infection in a patient on effective antiretroviral therapy
Patient

• 50 year old HIV-infected man
• Stable combination antiretroviral therapy (CART) X 9 years
  - No pre-treatment resistance mutations in plasma
    • Tenofovir
    • Emtricitabine
    • Atazanavir-ritonavir
  - Undetectable plasma HIV RNA
• 2 months of gait ataxia, headache, memory loss

Béguelin C. et al. OFID 2015
T-2 Weighted MR Brain

Béguelin C. et al. OFID 2015
Laboratory Data

- Plasma HIV RNA <20 c/ml
- CD4 790 (28%)
- CSF
  - WBC 75 cells/ul
  - Protein 99 mg/dl
  - CSF HIV RNA 1184 c/ml
    - M184V, K65R, K103N mutations
- Neuropsychological testing abnormal
  - Minor neurocognitive disorder
Course

• CART change
  - Zidovudine
  - Lamivudine
  - Darunavir-ritonavir
  - Raltegravir

• Clinical improvement
Three things to note: diagnosis is based on CSF, CNS ≠ CSF, and all “CNS escape” is not the same.
Source of CSF HIV?

• Early in infection
  - Derived from blood
  - Trafficking CD4+ T cells and monocytes
  - R5 and T-tropic
  - Centered in meninges
  - CSF pleocytosis
  - *Non-compartmentalized, equilibrated*
    - CART control of peripheral virus controls CSF virus

Source of CSF HIV?

- Later in infection (hypothesis)
  - R5 and M-tropic
  - Infection of brain macrophages and microglia
  - *Compartmentalized*
    - Requires local antiretroviral concentrations sufficient to control virus in brain

Systemic CART is largely effective in treating CSF HIV

<table>
<thead>
<tr>
<th>2010 CPE Rank</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
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<tbody>
<tr>
<td>NRTIs</td>
<td>Zidovudine</td>
<td>Abacavir</td>
<td>Didanosine</td>
<td>Tenofovir</td>
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<td></td>
<td>Emtricitabine</td>
<td>Lamivudine</td>
<td>Zalcitabine</td>
<td>Stavudine</td>
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<td>NNRTIs</td>
<td>Nevirapine</td>
<td>Delavirdine</td>
<td>Etravirine</td>
<td>Efavirenz</td>
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<tr>
<td>PIs</td>
<td>Indinavir-r</td>
<td>Darunavir-r</td>
<td>Atazanavir-r</td>
<td>Nelfinavir</td>
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<td></td>
<td>Fosamp-r</td>
<td>Atazanavir</td>
<td>Ritonavir</td>
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<td></td>
<td>Indinavir</td>
<td>Fosamp</td>
<td>Saquinavir-r</td>
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<td></td>
<td>Lopinavir-r</td>
<td>Saquinavir</td>
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<td>Tipranavir-r</td>
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<td>Fusion/Entry</td>
<td>Maraviroc</td>
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<td>Enfuvirtide</td>
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<tr>
<td>Integrase</td>
<td>Raltegravir</td>
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Higher CPE Regimens More Effectively Suppress CSF HIV RNA

Letendre S. Top Antivir Med 2011;19
Predicting Detectable CSF HIV RNA

  - Modeled probability of detectable CSF HIV RNA in 1053 CHARTER participants on CART
  - Devised a “CSF HIV risk score” (0-42 points)
    - CPE: 0, 6, 9 points
    - Race: 0, 3, 4 points
    - Current depression: 0, 4 points
    - CART adherence: 0, 3, 3 points
    - Plasma HIV RNA: 2, 2, 10, 18 points
    - CART months: 0, 2, 3, 4 points
Predicting Detectable CSF HIV RNA

OR detectable CSF HIV RNA 1.26 (1.21-1.31) per 1-point increase in score

CSF Escape

• Symptomatic
• Asymptomatic
• Secondary
Symptomatic CSF Escape

- Presumed to reflect virological failure in CNS
  - New or progressive neurological symptoms and signs
  - CSF pleocytosis

<table>
<thead>
<tr>
<th>HIV RNA</th>
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<tbody>
<tr>
<td>Plasma</td>
<td>CSF</td>
</tr>
<tr>
<td>&lt;50 c/ml</td>
<td>&gt;50 c/ml</td>
</tr>
<tr>
<td>50-500 c/ml</td>
<td>&gt; 2 X plasma</td>
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Treatment of Symptomatic CSF Escape

• Optimize CART
  - Ideally based on CSF resistance pattern
• Empirically increase CPE?
Asymptomatic CSF Escape: CSF Blips? No Change in CART recommended

- Edén A. et al. JID 2010;202
  - 69 neurologically asymptomatic or stable HIV-infected
    - CART X > 6 mo.
    - Plasma HIV RNA <50 c/ml
  - 7 (10%) detectable CSF HIV RNA
    - Median 121 c/ml (IQR 54-213)
    - Not related to CPE of CART regimen
    - Longer duration of CART
    - More treatment interruptions
    - More plasma blips
    - Higher CSF neopterin
      - Measure of immune activation
Secondary CSF Escape

- Superimposed CSF or CNS infection or inflammation
  - Influx of CD4+ T cells into CSF that are susceptible to HIV infection
    - Syphilis
    - Lyme
    - Varicella zoster
  - Accompanied by pleocytosis
  - Unclear significance
  - No change in CART recommended

Summary

• Symptomatic CSF escape is probably uncommon
  - Likely reflects loss of control of CNS virus
  - Should be explored in patients on therapy with new neurological symptoms and signs
  - May improve with CART optimization
    • Ideally based on genotype

• Asymptomatic CSF escape may be common
  - CSF “blips”? 
  - CART change not recommended
  - Unknown prognosis

• Secondary CSF escape
  - Epiphenomenon of CSF or CNS infection or inflammation
  - CART change not recommended