HIV: New onset seizures & Epilepsy

Hannah Cock
Professor of Epilepsy & Medical Education

SSAfrica Teaching Course, Mozambique 2016
Declaration

Dr Cock has received:

– Hospitality from all major AED manufacturers
– Invited talks & honoraria for UCB Pharma, Janssen-Cilag, Sanofi-Synthelabo, GSK, Eisai, Novartis
– Unrestricted Research Grants from UCB Pharma, Johnson&Johnson & Pfizer

http://www.whopaysthisdoctor.org/

This presentation reflects the views of author
Overview

• Epidemiology
• New onset seizures
  – Diagnostic Approach
  – Management
• Epilepsy
  – AEDs
  – Antiretroviral Therapy
**Epidemiology**

Epidemiology, causes, and treatment of epilepsy in sub-Saharan Africa

- **SSA High Incidence Epilepsy**
  - 81.7 per 100,000 (95% CI 28.0–239.5) vs 45.0 (30.3–66.7)

- **Up to 13% due to CNS infections**
  - Neurocystercercosis > Malaria > others

- **Acute symptomatic Sz**
  - Worldwide incidence 29-39/100,000/yr
  - In HIV+ve up to 20% (200,100,000/yr)
  - HIV Risk factor for Convulsive SE

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Awa Ba-Diop, Benoît Marin, Michel Druet-Cabanac, Edgard B N'goungou, Charles R Newton, Pierre-Marie Preux

Hauser and Beghi, Epilepsia, 2008; Sikazwe et al., Hiv Medicine, 2016; Kariuki et al., Neurology, 2015
# New onset Seizures & HIV

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>N</th>
<th>Incidence</th>
<th>Status Ep</th>
<th>GTCS</th>
<th>Epilepsy</th>
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<td>100</td>
<td>12</td>
<td>65</td>
<td>70</td>
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</tr>
<tr>
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<td>11</td>
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<tr>
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<td>20</td>
<td>8</td>
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<td>78</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>2012</td>
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<td>27</td>
<td>8 (paed)</td>
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<tr>
<td>2015</td>
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</table>

## Causes of Seizures in HIV

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>N</th>
<th>Toxo</th>
<th>Crypto</th>
<th>PML</th>
<th>Viral</th>
<th>Lymph</th>
<th>NK*</th>
<th>Other</th>
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<td>100</td>
<td>28</td>
<td>13</td>
<td>1</td>
<td>3</td>
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<td>1997</td>
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<td>8</td>
<td>6</td>
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<tr>
<td>2005</td>
<td>India</td>
<td>99</td>
<td>23</td>
<td>41</td>
<td>1</td>
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<td>3</td>
<td>44</td>
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<td>2008</td>
<td>Germany</td>
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<td>21</td>
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<tr>
<td>2009</td>
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<td>37</td>
<td>3</td>
<td>3</td>
<td>3</td>
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<td>27</td>
<td>54</td>
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<tr>
<td>2014</td>
<td>Zambia</td>
<td>95</td>
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<td>14</td>
<td>8</td>
<td>40</td>
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<tr>
<td>2015</td>
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<td>3</td>
<td>41</td>
<td>6</td>
<td>0</td>
<td>18</td>
<td>32</td>
</tr>
</tbody>
</table>

*Includes HIVEnceph
Other: Stroke, Metabolic; **TB**; Neurosyphillis; Drug toxicity

Holtzman et al., American Journal of Medicine, 1989; Dore et al., Journal of Neuro-AIDS, 1997; Sinha et al., Neurology Asia, 2005; Modi et al., Epilepsia, 2009; Kalungwana et al., American Journal of Tropical Medicine and Hygiene, 2014
Seizures in context HIV

- High likelihood neuropsychiatric & cognitive impairments (50%) in adults
- Associated with Neurological deficits (13%) and Developmental delay (50%) in children

Kalungwana et al., American Journal of Tropical Medicine and Hygiene, 2014
Samia et al., Journal of Child Neurology, 2013
New onset seizures in HIV
Diagnostic approach

• Well or ill?
  – Fever; meningism; confusion/LoC; rash

• Focal Neurological signs
  – Focal weakness/sensory loss
  – Cranial neuropathies
  – Retinopathy?

• Background
  – FH, Febrile Convulsions, TBI etc..
  – Medication
  – Development/cognitive function
Initial Investigations

• Bloods
  – Ca^{++}, Mg^{++}, Na^{+}
  – Full blood count, CRP

• CSF
  – Recommended in all even if afebrile
  – Cell, Protein, Sugar
  – Additional if available
    • India Ink, Gram, Culture, CrypAg, Cytol,
    • PCR TB, JCV, CMV, VZV, HSV, HIV load, ToxoAb
CT before LP?

- CT prior to LP if
  - Decreased level of consciousness
  - Focal signs
  - Papilloedema
  - Preceding seizures
  - Impaired immunity

CT First
- Diagnosis
- Safety

LP Delay
- Lifethreatening

Hasbun et al. NEJM 2001; Moolla et al., Southern African Journal of HIV Medicine, 2015
CT before LP?

- Early LP (Pre CT) may be justified
- Cross sectional observational study, SA
- 100 or 132 CT requests/12m, HIV+ve, Seizures
  - 99 No comment re papilloedema
  - 55 Abnormal: Active SOL(12), Oedema(13), Brain shift (5)
  - 68 had LP (35 before CT), 24% Abn (75% Meningitis)
  - 9 deaths (5 from meningitis); none from LP

<table>
<thead>
<tr>
<th>Feature</th>
<th>Prevalence Ratio (95%CI)</th>
<th>P (*sig multivar)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4&lt;200 (*50)</td>
<td>2-7 (3.7) (2.1-6.6)</td>
<td>0.0017 (*0.0001)</td>
</tr>
<tr>
<td>Focal Signs</td>
<td>3.8 (2.2-6.7)</td>
<td>0.0001</td>
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<tr>
<td>Vomiting</td>
<td>3.3 (1.7-6.4)</td>
<td>0.0184</td>
</tr>
<tr>
<td>GCS&lt;15</td>
<td>2.9 (1.4-5.9)</td>
<td>0.0020</td>
</tr>
<tr>
<td>No ICP features</td>
<td>0.2 (0.1-0.5)</td>
<td>0.0002</td>
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</table>
## CSF

<table>
<thead>
<tr>
<th>Look</th>
<th>Lymphocytes</th>
<th>Polymorphs</th>
<th>Protein</th>
<th>Glucose Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal/HIV</td>
<td>Clear</td>
<td>&lt;5/ &lt;50</td>
<td>0</td>
<td>0.2-4g/L</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Turbid/purulent</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Viral</td>
<td>Clear/Turbid</td>
<td>↑ (20-300)</td>
<td>0</td>
<td>n/↑</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>Clear/Turbid</td>
<td>↑ (20-200)</td>
<td>0</td>
<td>n/↑</td>
</tr>
<tr>
<td>TBM</td>
<td>Turbid/Viscous</td>
<td>↑↑ (100-500)</td>
<td>0 / sl↑</td>
<td>↑↑↑</td>
</tr>
</tbody>
</table>

– May identify treatable cause in ~25%
– Frequently not done/declined
– nt/cognitive function

Sikazwe et al., Hiv Medicine, 2016
Imaging

- Cohort Study HIV-Associated Seizures and Epilepsy (CHASE, Zambia)
  - N=43/95 with no other cause (inc CSF)
  - 80% Advanced disease; 44% opportunistic infection
  - 70% Abnormal imaging
    - 56% White matter (mostly Vasogenic Oedema)
    - Deep Gray (19%); Post fossa (21%); Cortical (28%)
    - 16% Atrophy
    - None predictive of seizure recurrence

Potchen et al., Neurology international, 2014
Cryptococcal Meningitis

1. Basal meningeal enhancement
2. Dilated Temp Horns
3. Effaced sulci
Toxoplasmosis

Neurological infections: HIV, www.ebrainjnc.com
CNS Lymphoma    PML

Price, Lancet, 1996
Normal CT

• ? Atrophy
  – HIV Encephalopathy
• ? Early disease (e.g. PML)

EEG

• Often unhelpful
• Non-specific/generalized slowing
New onset seizures in HIV

CT

Focal +ve

Toxoplasmosis
PML
Lymphoma
Tuberculoma

Focal -ve

Crypto meningitis
TB Meningitis

CSF

normal

Abnormal

HIV Per se
Metabolic

Crypto Mening

India Ink
Crypto Ag
Crypto culture

TB Mening

TB Cult
AFB
Elisa/PCR TB

Other meningitis

Toxoplasmosis

Toxo Ab

Treat Op Infection; ARV (NB Interactions)

Satishchandra and Sinha, Epilepsia, 2008
AED Treatment

– Status Epilepticus Rx takes priority over ARV
– For others, may not be needed at all or for short term (3-6m) only
– General Population recurrence data may not be valid in HIV population

Unknown Cause

- Low Viral, Hi CD4 → No AED
- Hi Viral, Low CD4 → Consider until

Reversible Cause

- Short Duration → No AED
- Medium Duration → Until 3-6m post

Irreversible Cause → AED

Siddiqi and Birbeck, Current Treatment Options in Neurology, 2013
## AED selection in HIV: ILAE/AAN guidelines

### Effect of AED on ARV

<table>
<thead>
<tr>
<th>AED/ARV</th>
<th>PI ARV</th>
<th>II ARV</th>
<th>N(N)RTI</th>
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<tbody>
<tr>
<td>PHT</td>
<td>Lop, Rit</td>
<td></td>
<td>Nev</td>
</tr>
<tr>
<td>CBZ</td>
<td></td>
<td>Efav, Nev</td>
<td></td>
</tr>
<tr>
<td>PB</td>
<td></td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>VPA</td>
<td>Lop, Rit, Ataz</td>
<td>Efav</td>
<td>Zid</td>
</tr>
<tr>
<td>LTG</td>
<td></td>
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<tr>
<td>BZD</td>
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<td>Zid</td>
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</table>

### Effect of ARV on AED

<table>
<thead>
<tr>
<th>ARV/AED</th>
<th>PHT</th>
<th>CBZ</th>
<th>PB</th>
<th>VPA</th>
<th>LTG</th>
<th>BZD</th>
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</thead>
<tbody>
<tr>
<td>PI ARV</td>
<td>Lop, Rit</td>
<td></td>
<td></td>
<td>Lop, Rit</td>
<td>Lop, Rit</td>
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</tr>
<tr>
<td>II ARV</td>
<td></td>
<td>Lop, Rit</td>
<td></td>
<td>Ralt</td>
<td>Ralt</td>
<td></td>
</tr>
<tr>
<td>N(N)RTI</td>
<td>Zid</td>
<td>Efa</td>
<td></td>
<td>Efav</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Virologic failure**
- EI-AEDs 63% vs 27%
- OR 4.58 (CI 1.47-14.25, p<0.009)

Okulicz et al., AIDS Res Th 2011

Birbeck et al., Neurology, 2012
AED selection in HIV: ILAE/AAN guidelines

• Level C* evidence:
  – May need to avoid EI AEDs with PI or NNRTIs, or monitor levels ARV to ensure efficacy
  – PHT: May need 50% inc Lopinavir/Ritonavir
  – VPA – may need lower Zidovudine dose
  – VPA and Efavirenz OK
  – Riton/Atazan may need inc LTG dose (Ralte/Atazan OK)

• Level U
  – Everything else!

*Expert opinion and panel consensus
HIV developing in known epilepsy

- ARV and AED co-administration unavoidable
- Careful choice ARV, and/or switch to alternative AED
- Low threshold repeat Investigation (MRI, CSF) if seizure deterioration
Botswana, Perinatal HIV infection, enrolled aged 0-18
- Confirmed HIV, at least 6m f/u, initiated cART
- Excluded HIV by other routes, Sz prior to cART
- Early Treatment: cART<12m, or CD4<25% to 5y, or <350m³ >5y
- 1244 Elligible, identified 29 cases and 58 matched controls.

ARV May prevent epilepsy?

<table>
<thead>
<tr>
<th>Retrospective case-control</th>
<th>Case (29)</th>
<th>Controls (58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at cART Rx (months, range)</td>
<td>72 (24-96)</td>
<td>70 (22-120)</td>
</tr>
<tr>
<td>WHO Stages 1-4 (%)</td>
<td>7-3-24-66</td>
<td>14-2-20-22</td>
</tr>
<tr>
<td>WHO no/mild-Ad-Sev IS (%)</td>
<td>21-21-59</td>
<td>31-10-29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Early Treatment</th>
<th>OR (95%CI)</th>
<th>p</th>
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<tr>
<td>1 (WHO def)</td>
<td>0.36 (0.14 - 0.92)</td>
<td>0.03</td>
</tr>
<tr>
<td>2 (CD4&lt;500&gt;5y)</td>
<td>0.37 (0.14 -1.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>3 (early vs late)</td>
<td>0.32 (0.13 - 0.76)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Bearden et al., J AIDS, 2015
Summary

• New onset seizures common in HIV
• Often Acute Symptomatic
  – Toxoplasma, Cryptococcus, TB, PML, encephalitis
• Remote symptomatic & HIVE also
• CT & LP ideally in all
  – clinical urgency/resource availability
• AEDs – avoid Eis/consider interactions
• ARV also important