Therapeutic dilemma: the use of Anticonvulsants in HIV positive individuals

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Interactive Pharmacology Case presentation workshop

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Case

- 30 years old male Caucasian
- Previously well
- Presented to A&E with a 1 week history of malaise and photophobia
- Generalised tonic-clonic seizure
- Continue having seizures and dropped GCS to 6/15
- Admitted to ITU

Case

- Loaded with phenytoin in ITU
- MRI head with contrast: normal
- LP: normal opening pressure, WBC< 1, glucose ratio: 0.7, protein 0.38mg/dL and no organisms
- Normal baseline investigations: Chest X Ray, FBC, U&Es, LFTs and CRP
- EEG: Normal
- Patient consented for HIV test:
  - HIV AB: equivocal (evolving serology)
  - Plasma HIV RNA: 927 500 copies/mL
• Working diagnosis:
  ▪ Primary HIV infection with CNS involvement

• 1 week later, discharged from hospital

• Transferred to outpatients at our centre:
  ▪ No HAART
  ▪ Phenytoin 300mg OD
  ▪ Left lower leg: weakness (4/5), reduced reflexes, normal plantar reflexes, normal sensation and coordination.
HIV investigations

- CD4: 355 cells/μL
- Plasma HIV RNA: 655,400 copies/mL
- CSF HIV RNA: 11,100 copies/mL
- Genotype from plasma and CSF:
  - Concordant
  - K103N, V106I (NNRTI resistance)
- HLA B5701 NEGATIVE
- Plasma CCR5 tropic V3 loop

Problems

- Primary HIV infection with CNS involvement
- NNRTI baseline resistance
- Ongoing neurological impairment
- Ongoing anticonvulsants with potential for drug-drug interactions with HAART
### What would be your plan?

1. Avoid HAART (due to phenytoin interactions)
2. Start HAART continue same dose phenytoin
3. Start HAART and stop anticonvulsant
4. Start HAART and switch anticonvulsant immediately
5. Start HAART continue phenytoin with a view to switching anticonvulsant gradually

### BHIVA guidelines 2008

Treatment in primary infection (outside a prospective study) should only be routinely considered in those with:

- **Neurological involvement**
- Any AIDS-defining illness
- A CD4 cell count persistently < 200 cells/uL (i.e. for 3 months or more)
**Which HAART?**

1. NRTI plus NNRTI
2. NRTI plus boosted PI
3. NRTI plus new agent
4. Novel regimen

**HAART options**

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<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>Protease I</th>
<th>Integrase I</th>
<th>Entry I</th>
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<tr>
<td>abacavir</td>
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Potential archived NRTI Resistance (in view of NNRTI resistance)  
NNRTI resistance  
Recognised drug-drug interactions with anticonvulsants  
Possible Drug interactions
Progress

Primary HIV
Week 0
Outpatients
Week 1
ARV, Phenytoin 200mg, Valproate 600mg

- Anticonvulsants:
  - Commenced sodium valproate
  - Gradual phenytoin reduction over 6 weeks (to prevent phenytoin withdrawal seizures)

- Antiretrovirals:
  - Trizivir one tablet BD
  - Raltegravir 400mg BD

- Neurology signs resolved 2 weeks later

Progress

Primary HIV
Week 0
Outpatients
Week 1
Skin rash
Week 5
ARV, Phenytoin 100mg, Valproate 1.5 gr

- Admitted to hospital
- Unwell, fever
- Skin:
  - Morbilliform rash with some purpuric lesions on trunk and lower limbs
  - Mild peri-orbital oedema
  - No mucosal lesions
### What is the most likely cause of the rash?

1. Abacavir hypersensitivity
2. Drug skin rash due to anticonvulsants
3. Drug skin rash due to antiretrovirals
4. Other

### Cause of Skin rash

- Skin biopsy consistent with drug reaction:

### Incidence of skin rash:

- Phenytoin: (12% between 3 to 8 weeks of drug initiation)
- Raltegravir: (1-10%)
- Zidovudine/Lamivudine: (<1%)
- Abacavir: (<1% in patients with negative HLA-5701)
- Sodium valproate: (<1%)
Phenytoin 100mg, Valproate 1.5 gr

Primary HIV
Week 0

Outpatients
Week 1

Skin rash
Week 5

• Antiretrovirals:
  • All stopped

• Anticonvulsants:
  • Stopped phenytoin
  • Commenced clobazam 10mg (to prevent phenytoin withdrawal seizures)
  • Continued sodium valproate
  • Skin improved after 1 week

What ARV regimen would you consider now?

1. NRTI-based HAART
2. NRTI plus PI based HAART
3. NRTI plus Maraviroc
4. Re-start previous regimen
### HAART options

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- Potential archived NRTI resistance
  - ? Skin rash

- Could be used because of manageable drug-drug interactions

- ? Skin rash

### Outcome

Commenced new HAART regimen:
- Maraviroc 150mg BD
- Kaletra two tablets BD
- Truvada one tablet OD

- CD4: 1380 cells/uL
- Plasma HIV RNA: <50 copies/mL
- On a sodium valproate discontinuation regimen
- No seizures
**Learning points**

1. Neurological involvement in the context of primary HIV infection is an indication for HAART treatment.

2. Close communication with neurology consultant is essential for the adequate management of HIV patients with seizures due to the complexity of drug to drug interactions.

3. Stopping anticonvulsants abruptly can lead to development of withdrawal seizures.

**Thanks to**

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