Opportunistic Infections

Dr. Edmund Wilkins
Head of the HIV Clinical Trials Unit
North Manchester General Hospital
“Support needing populations through medical assistance and the transfer of knowledge to local medical practitioners.”

Our vision for the Medical Assistance & Medical Education (MAME) Programs
Outline

• Background

• Today I will break it down:
  • Review of many of the OI’s
  • Focus on the main clinical challenges
  • Present recent data

• Please interrupt......
In the West! HOPS Cohort: Late presentation and opportunistic infections (OIs)

- With the advent of cART and routine use of antimicrobial prophylaxis, the rates of AIDS-defining OIs among HIV-infected have declined dramatically.
- Nonetheless, OIs remain a leading cause of hospitalization and death among late presenting patients.

Adapted from Buchacz K et al., *AIDS* 2010, 24:1549–1559.

During 2003–2007 there were no significant changes in annual rates of OI.

A third of OIs were diagnosed at CD4 ≤200 cells/mm³.
Often difficult to diagnose

- Basic demographics
- History
- Standard lab tests
- Therapeutic trials
- Second opinion
- Literature review
- Serology
- Age
- Biopsy results
- Cultures

Diagnosis!
May be part of multiple infections requiring treatment
Risk of opportunistic infections by CD4 count

Moderate immunodeficiency
- Lymphadenopathy
- Thrombopenia
- Oral hairy leukoplakia
- Herpes zoster
- Oral thrush
- Cervical dysplasia
- Cervical carcinoma
- Recurrent bacterial pneumonia
- Tuberculosis
- Kaposi’s Sarcoma

Severe immunodeficiency
- Candida oesophagitis
- *Pneumocystis jiroveci* pneumonia
- Malignant lymphoma
- Persistent ulcerous Herpes simplex
- Cerebral toxoplasmosis
- Cryptosporidiosis
- HIV-encephalopathy
- Histoplasmosis

Profound immunodeficiency
- Progressive multifocal leukoencephalopathy
- Cryptococcosis
- Cytomegalovirus retinitis
- Disseminated *Mycobacterium avium* infection
- Disseminated *Mycobacterium genavense* infection

Adapted from Battegay M et al., *Antivir Ther* 2007, 12:841–851.
Guidelines exist..
OI’s in the Brain
Patient 1

- 37-year male from SSA
- Headaches and fever for 2w
- Focal fit at work Jan 2009
- HIV +ve
- CD4 102
- Further focal fits
- Mild weakness left lower limb
What is your diagnosis?

1. Cerebral Abscess
2. Primary CNS lymphoma
3. Cerebral toxoplasmosis
4. Tuberculoma
5. Cryptococcoma
Patient 1

- 37-year male from SSA
- **Headaches and fever for 2w**
- **Focal fit at work Jan 2009**
- HIV +ve
- **CD4 102**
- Further focal fits
- **Mild weakness left lower limb**
Patient 1

- 37-year male from SSA
- Headaches and fever for 2w
- Focal fit at work Jan 2009
- HIV +ve
- CD4 102
- Further focal fits
- Mild weakness left lower limb
- MR scan performed
Clinical challenges with toxoplasmosis

A. Diagnosis without/with scans
B. Optimal treatment
C. Steroids and biopsy
D. Persistent changes on scan
E. When to start ART
F. Distinguishing relapse from IRS
1. Diagnosing cause – clinical toxoplasmosis

<table>
<thead>
<tr>
<th></th>
<th>TOXOPLASMOSIS</th>
<th>PCNSL</th>
<th>PML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
<td>Headache, focal fits, <strong>fever, drowsy</strong>, focal neurology</td>
<td>Confusion, focal neurology</td>
<td>Visual/speech defects, focal neurology</td>
</tr>
<tr>
<td>Seizures</td>
<td><strong>33%</strong></td>
<td><strong>15%</strong></td>
<td>Uncommon</td>
</tr>
<tr>
<td>Clinical history</td>
<td>&lt;2 weeks</td>
<td>2-8 weeks</td>
<td>Weeks to months</td>
</tr>
<tr>
<td>CD4 count</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;50</td>
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<tr>
<td>Other</td>
<td>Retinitis may coexist Rarely encephalitic process</td>
<td>No evidence of disease outside of brain</td>
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</table>
1. Diagnosing cause - imaging

<table>
<thead>
<tr>
<th>MR FEATURES</th>
<th>PCNSL</th>
<th>TOXOPLASMOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Single-few</td>
<td>Usually multiple</td>
</tr>
<tr>
<td>Enhancement</td>
<td>Prominent</td>
<td>Prominent Ring</td>
</tr>
<tr>
<td>Oedema</td>
<td>Mild-moderate</td>
<td>Marked</td>
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<tr>
<td>Location</td>
<td>Periventricular, Basal ganglia, Brain stem, Cortical</td>
<td>Basal ganglia, Brain stem, Cortical</td>
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<tr>
<td>MR T1</td>
<td>Low to isodense</td>
<td>Interface grey-white matter</td>
</tr>
<tr>
<td>MR T2</td>
<td>Variable</td>
<td>Low signal</td>
</tr>
<tr>
<td></td>
<td>Variable</td>
<td>High signal</td>
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1. Differential diagnosis
Primary CNS lymphoma

<table>
<thead>
<tr>
<th>CLINICAL FEATURES</th>
<th>Primary CNS Lymphoma</th>
<th>Toxoplasmosis</th>
<th>PML</th>
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</thead>
<tbody>
<tr>
<td>Presentation</td>
<td>Confusion, focal neurology, <strong>no fever</strong></td>
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1. Differential diagnosis - PCNSL

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## 1. Differential diagnosis - PML

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<td>White matter</td>
<td>Brain stem</td>
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<td></td>
<td></td>
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<td>High signal</td>
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Advice given for immediate management options

1. Treat for toxoplasmosis
2. Defer treatment and get CSF
3. Refer to unit where they can do urgent brain biopsy
4. Treat for TB
5. Treat for toxoplasmosis and give steroids
6. Other

Audience vote
Patient with toxoplasmosis after 2w toxoplasma treatment
Back to our patient post treatment at 8w
Patient with PCNSL after 2w toxoplasma treatment
Additional imaging

- 201 Thallium SPECT
- 18FDG-PET (positron emission scanning):
  - Lesions show increased uptake
  - Toxoplasmosis lesions are metabolically inactive

- Brain biopsy

![18FDG-PET](image)
2. Diagnosing cause - the CD4 count

- 28yr old Zimbabwean lady
- In UK for 3 years
  - Diagnosed HIV +ve at antenatal screening
  - Currently on EFV/TDF/FTC
  - CD4 876, VL <40 c/ml
- Admitted after having 2 GM convulsions at home
  - No history of fits or other neurological problems, TB
What is your diagnosis?

1. Cerebral Abscess
2. Primary CNS lymphoma
3. Cerebral toxoplasmosis
4. Tuberculoma
5. Cryptococcoma
6. Other
2. Diagnosing cause - the CD4 count

• 28yr old Zimbabwean lady
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  – CD4 876, VL <40 c/ml
• Admitted after having 2 GM convulsions at home
  – No history of fits or other neurological problems, TB
The importance of the CD4...

CD4 876 cells/µl
Neurocystercocosis..

Serology strongly +ve T. Solium CC

• Started anti-convulsants
• Treated with:
  – Steroids 5d
  – Albendazole 14d

• No real association with HIV
• Can occur at any CD4

LESSON: THINK NON-HIV IF HIGH CD4
The importance of the CD4 count and a brain biopsy

- Known HIV +ve
  - CD4 333
- Admitted 2w hx of ↑ psychosis
  - CRAG -ve
  - CSF 84 LC: protein 1.2, no growth
- Treatment:
What is your diagnosis?

1. TB meningitis
2. Cryptococcal meningitis
3. Listeria meningitis
4. Viral meningitis
5. Toxoplasmosis
6. Other
The importance of the CD4 count and a brain biopsy

- Known HIV +ve
  - CD4 333
- Admitted 2w hx of ↑ psychosis
  - CRAG -ve
  - CSF 84 LC: protein 1.2, no growth
  - PCR’s -ve

- Treatment:
  - Acyclovir, Ceftriaxone
  - TB treatment (RBT), steroids 4w
  - DAR/r/TDF/FTC

- No improvement clinically
  - CSF 230 mixed; protein 1.4
The importance of the CD4 count and a brain biopsy

- Known HIV +ve
  - CD4 333
- **Admitted 2w hx of↑ psychosis**
  - CRAG -ve
  - CSF 84 LC: protein 1.2, no growth
  - PCR’s -ve
  - MR: Meningeal thickening
- Treatment:
  - Acyclovir, Ceftriaxone
  - TB treatment (RBT), steroids 4w
  - DAR/r/TDF/FTC
- No improvement clinically
  - CSF 230 mixed; protein 1.4
- **MR scan after 3 weeks**
Thought to be mad?

- TB treatment intensified
- Toxoplasma treatment started:
  - SD and pyrimethamine/FA
  - No improvement MR scan
- Neurosurgeons biopsied

Remember CD4 333
What is your diagnosis?

1. Cerebral toxoplasmosis
2. Cryptococcoma
3. Candida brain abscess
4. Cerebral aspergillosis
5. Tuberculosis
The importance of the CD4 count and a brain biopsy

- TB treatment intensified
- Toxoplasma treatment started:
  - SD and pyrimethamine/FA
  - No improvement MR scan
- Neurosurgeons biopsied

- Culture: Aspergillus *fumigatus*

- Started Voriconazole
After 12w of antifungal treatment..
3. Diagnosing cause - serology and CSF?

- **Toxoplasmosis IgG antibody:**
  - +ve 20-80% depending on age and regional exposure
  - 1% seroconversion annually
  - Up to 15% may be IgG antibody -ve

- **Toxoplasma PCR CSF:**
  - Sometimes not possible because of ↑ ICP
  - Sensitivity 95% specificity 95%
What treatment would you start?

- Co-trimoxazole
- Pyrimethamine and sulphadiazine
- Pyrimethamine and clindamycin
- Atovaquone
- Azithromycin and Atovaquone
- Other
B. What is optimal treatment

- 2 RCT comparing SUL/PYR vs. CLIND/PYR 6w

<table>
<thead>
<tr>
<th></th>
<th>N= 59</th>
<th>N= 292</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clind/Pyr</td>
<td>Sulph/Pyr</td>
</tr>
<tr>
<td>Response (%)</td>
<td>65</td>
<td>70</td>
</tr>
<tr>
<td>Toxicity D/C (%)</td>
<td>23</td>
<td>33</td>
</tr>
</tbody>
</table>

- Other small RCT confirm activity of:
  - ATOV or AZITH or CLARITH/AZITHRO or DOXY or DAPSONE with PYR and FOL
  - ATOV and SULP or Minocycline or alone
What is optimal treatment

- Overall risk of progression higher in patients receiving PM-CM than PM-SD.
- No difference during acute therapy
- Relapse rate twice as high
- Toxicity rates less with PM-CM
- Studies mainly pre-ART

Overall progression of disease

PM/SD = pyrimethamine/sulphadiazine
PM/CM = pyrimethamine/clindamycin
Co-trimoxazole as 2\textsuperscript{nd} line

- Single randomized controlled study of CTX
  - 40 received CTX
  - 37 received PYR-SULPH
- PYR-SULPH and CTX were equivalent with respect to clinical and radiological efficacy
  - 85.7\% vs. 83.7\% and 69.6\% vs. 72.9\%
- However, tolerability significantly better in the CTX group
  - 5 events in the CTX group vs. 14 events in the PYR-SULPH group
- Two single arm cohort studies have repeated these results for CTX
Toxoplasmosis – treatment

- Repeat imaging after 2-4w therapy of pyrimethamine/folinic acid with either sulphadiazine or clindamycin
- Clinical improvement:
  - 50% at 5d, 70% at 7d and 90% at 14d of toxoplasma treatment
  - Failure to improve at 2w indicates likely PCNSL
- MRI improvement:
  - Seen by 2-4w
Do you advise steroids?

- Always
- Only when significant localising signs
- Only when oedema (if you can get scan)
- Never
- Only if deteriorates on treatment
- Other

Audience vote
C. What is the place of brain biopsy & steroids?

• Consider brain biopsy when:
  – **Empiric therapy fails**
  – There is a reliable history of co-trimoxazole prophylaxis
  – Patients receiving steroids relapse on tailing off
  – **There is a single atypical lesion,**
  – The CD4 count is >200 cells/mL

Biopsy diagnosis = TB
What is the place of brain biopsy & steroids?

• Dexamethasone indicated:
  – If features of significant raised ICP or midline/tentorial shift
  – Dexamethasone 4mg qds tapering dose
  – Can cloud diagnosis and management
  – Clinical deterioration after tailing off steroids usually indicates urgent need for brain biopsy
D. How to manage persistent changes on scan/persistent neurology

• Heterosexual man presents with:
  – Convulsions, fever, localising signs
  – Diagnosed as bacterial abscess
  – 3w before HIV diagnosed and toxoplasmosis treated

• Started ART at 3 weeks
• Now CD4 >350
Progress at 4 and 8 weeks – biopsy showed ‘inflammation’
At 6 months – biopsy reviewed

- Where a diagnosis is uncertain – consider biopsy
- Changes may take years to resolve or never do so
When would you start ART?

- Immediately
- When established on toxoplasma therapy
- Around 2 weeks
- After discontinuing toxoplasma treatment at around 6w
- Not before 3 months
Starting HAART: ACTG 5164: Immediate vs. deferred in patients with acute OIs (not TB)

- Immediate treatment group had reduced rate of AIDS progression or death (14.2%) compared with deferred treatment group (24.1%)
- No differences in IRIS between arms (10 immediate vs. 13 deferred)
  - However, 70% of patients with PCP received corticosteroids
- The most common OIs were PCP (63%), Cryptococcus (12%), BI (bacterial infection (11%)), TB excluded

Adapted from Zolopa A, et al. CROI 2008, Boston, MA, USA, Abstract 142
E. Distinguishing relapse from IRS

Pre-treatment  Week 1  Week 6 (3w after ARV)
Distinguishing relapse from IRS

- IRS with ART
  - Uncommon
  - Adherence good
  - 4-8w after starting ART
  - Rapid CD4 rise
  - Significant oedema
- Biopsy may be required
- Treatment steroids
Patient 2

- 41y old male
- Poor adherence HAART
- **CD4 30-70**
- **Severe headache**, tiredness 2-3 weeks
- Occasional double vision
- No localising signs, no neck stiffness
What is your diagnosis?

1. TB meningitis
2. Cryptococcal meningitis
3. CMV encephalitis
4. Viral meningitis
5. Toxoplasmosis
6. Tuberculoma
7. Primary CNS lymphoma
Patient 2

- 41y old male
- Poor adherence HAART
- **CD4 30-70**
- **Severe headache**, tiredness 2-3 weeks
- Occasional double vision
- No localising signs, no neck stiffness
- CSF
  - Protein 0.8, glucose 2.1
  - Lymphocytes 85, RBC 5
  - **India ink +ve, culture cryptococcus**
  - Pressure 32 mmHg
- CT scan
Patient 2

- 41y old male
- Poor adherence HAART
- CD4 30-70
- Severe headache, tiredness 2-3 weeks
- Occasional double vision
- No localising signs, no neck stiffness
- MR scan
- CSF
  - Protein 0.8, glucose 2.1
  - Lymphocytes 85, RBC 5
  - **India ink +ve, culture cryptococcus**
  - Pressure 32 mmHg
### Symptoms + CSF parameters

<table>
<thead>
<tr>
<th>Duration of symptoms — days</th>
<th>15</th>
<th>14</th>
<th>12</th>
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</thead>
<tbody>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>7–22</td>
<td>8–18</td>
<td>7–20</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptom</th>
<th>95/97 (98%)</th>
<th>99/99 (100%)</th>
<th>98/99 (99%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache — no./total no. (%)</td>
<td>75/97 (77%)</td>
<td>75/98 (77%)</td>
<td>72/98 (73%)</td>
</tr>
<tr>
<td>Fever — no./total no. (%)</td>
<td>66/91 (73%)</td>
<td>64/91 (70%)</td>
<td>66/95 (69%)</td>
</tr>
<tr>
<td>Neck stiffness — no./total no. (%)</td>
<td>9/94 (10%)</td>
<td>9/98 (9%)</td>
<td>2/98 (2%)</td>
</tr>
<tr>
<td>Seizure — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale score — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>66/97 (68%)</td>
<td>67/99 (68%)</td>
<td>78/98 (80%)</td>
</tr>
<tr>
<td>11–14</td>
<td>21/97 (22%)</td>
<td>24/99 (24%)</td>
<td>15/98 (15%)</td>
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<tr>
<td>≤10</td>
<td>10/97 (10%)</td>
<td>8/99 (8%)</td>
<td>5/98 (5%)</td>
</tr>
<tr>
<td>Cranial-nerve palsy — no./total no. (%)</td>
<td>27/97 (28%)</td>
<td>22/98 (22%)</td>
<td>18/98 (18%)</td>
</tr>
<tr>
<td>Papilledema — no./total no. (%)</td>
<td>18/85 (21%)</td>
<td>19/89 (21%)</td>
<td>17/93 (18%)</td>
</tr>
<tr>
<td>CSF opening pressure &gt; 18 cm of CSF — no./total no. (%)</td>
<td>56/83 (67%)</td>
<td>61/80 (76%)</td>
<td>55/81 (68%)</td>
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<table>
<thead>
<tr>
<th>CSF white-cell count — cells/ml</th>
<th>33</th>
<th>26</th>
<th>24</th>
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<td>8–61</td>
<td>7–83</td>
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# Cryptococcal and TB meningitis

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<th><strong>TB meningitis</strong></th>
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<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td><strong>Headache, fever, drowsy, confusion, eye symptoms</strong></td>
<td><strong>Headache, fever, confusion, CN palsies, neck stiffness</strong></td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td>15%</td>
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<tr>
<td><strong>Clinical history</strong></td>
<td>&lt;4 weeks</td>
<td>1-8 weeks</td>
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<tr>
<td><strong>Masses</strong></td>
<td>Rare Single</td>
<td>Uncommon May be multiple</td>
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<td><strong>Enhancement</strong></td>
<td>Marked meninges</td>
<td>Marked basal meninges</td>
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<tr>
<td><strong>Hydrocephalus</strong></td>
<td>Occasional</td>
<td>Occasional</td>
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<tr>
<td><strong>Location masses</strong></td>
<td>Basal ganglia</td>
<td>Anywhere</td>
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# Cryptococcal meningitis

<table>
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<tr>
<th>Other features</th>
<th>Cryptococcal meningitis</th>
<th>TB meningitis</th>
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<tbody>
<tr>
<td></td>
<td>Lymphocytes</td>
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</tr>
<tr>
<td></td>
<td>High protein</td>
<td>AFB rarely +ve</td>
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<tr>
<td></td>
<td>India ink +ve</td>
<td>PCR +ve</td>
</tr>
<tr>
<td></td>
<td>CRAG +ve</td>
<td>CXR +ve</td>
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Clinical challenges

A. Raised ICP
B. Persistence vs. relapse vs. IRS
C. Optimal treatment
D. Fluconazole resistance
E. When to start ART
F. CRAG +ve and asymptomatic
A. Raised ICP
A. Raised ICP

- **Always** measure opening pressure at LP
  - If opening pressure > 25 cm H2O drain until < 20cm or 50% of initial pressure
  - Repeat daily until stable
  - Always consider repeat LP on patient who deteriorates or develops new neurological signs
  - In resistant cases consider lumbar drain or VP shunt
  - No evidence for benefit from steroids or acetazolamide
  - Higher burden CRY gives higher pressures

**LESSON: LP – CRAG and pressure**
What treatment would you start?

1. Fluconazole alone
2. Amphotericin B & 5-flucytosine
3. Amphotericin B & fluconazole
4. Voriconazole alone
5. Fluconazole & 5-flucytosine
6. Amphotericin and itraconazole
Optimal treatment

AmpB vs. AmpB/5FU vs. AmpB/FLU
Our patient

- After 3w therapy with AMP-B and high-dose FLU and then oral therapy for 1 week
- Readmitted:
  - India Ink +ve
  - Protein decreased to 0.6
  - WCCT 43 cells/ml
What would you do?

1. Restart same dose of same therapy
2. Give higher dose AMP-B
3. Give 5FU with AMP-B
4. Await CSF culture
5. Give steroids
6. Start ART

Audience vote
B. Persistence vs. Relapse vs. IRS

• Persistence:
  – \( \geq 4w \) still positive culture despite therapy
  – Usually due to suboptimal induction therapy
  – India Ink and CRAG titre no help

• Relapse:
  – **Return of +ve culture after negative cultures** from sterile site (CSF)
  – And usually return of symptoms/signs
B. Persistence vs. Relapse vs. IRS

**Persistence**
- **Reinstitute induction therapy**
- Consider increasing AMPB or FLU dose or duration of induction phase
- Check changes in MIC as fluconazole resistance may have developed
- Consider alternative combinations

**Relapse**
- **Restart induction therapy**
- Check changes MIC for fluconazole resistance
- Consider higher dose of maintenance drug
B. Persistence vs. Relapse vs. IRS

**IRS**

- Unmasking and paradoxical
- Varies in severity
- Identical presentation to relapse
- Associations:
  - Presenting diagnosis, low CD4, high CRAG titre, lack of previous ART, rapid decrease in VL
  - Negative CSF culture
  - Higher cell count

**Management**

- Exclude active CRY disease
- Continue CRY treatment
- Continue ART
- Consider steroids in severe disease
- Monitor ICP
Cryptococcal IRS

- IRS: 25%
- Associated with:
  - CRAG +ve
  - Culture +ve
  - Faster CD4 rise
D. Fluconazole resistance

• Where possible isolates should be sent for MIC testing
  – <16 = susceptible
  – 16-32 = susceptible at high doses (many would consider using alternative azole)
  – >64 = resistant

• Relapsing disease
  – N=30
  – Majority developed fluconazole resistance
E. When to start ART?

- Immediately <72 hours
- As soon as the patient is stabilised <2w
- At the end of induction therapy = 2w
- When the India ink stain becomes negative
- When the CSF pressure is normal
- When the CSF is culture negative
- At the end of maintenance treatment = 8w
- Other

Audience vote
When to start? Decreased survival rate starting early

- N = 177
- Arms randomised to start therapy at 1-2w or 5w
- Induction treatment AMP-B/FLU 800mg for 2w
- Consolidation therapy FLU
- Early ART resulted in higher mortality HR 1.73 (1.62-2.83)
- Associated with fewer CSF white cells at BL
E. When to start? Increased survival rate starting early

- N = 501
- Meta-analysis
- Multiple sites
- Mortality
  - 17% at 2w
  - 34% at 4w
- IRS no association with
  - Death
  - ART timing
F. CRAG +ve and asymptomatic

• Check blood and CSF cultures
• If culture +ve give full treatment and then secondary prophylaxis
• If culture –ve,
  – Either maintain on fluconazole prophylaxis until immune reconstitution
  – Or treat with full dose fluconazole
Patient

• 39y old diagnosed 2004
• Not seen clinic for many years
  – No HAART
  – **Rapid dementing / encephalopathy illness**
  – **CD4 14**, viral load 2 million, **CRAG -ve**

• Admitted:
  – CSF 320 white cells
  – Raised protein
What is your diagnosis?

1. TB meningitis
2. Cryptococcal meningitis
3. CMV encephalitis
4. Viral meningitis
5. Toxoplasmosis
6. Tuberculoma
7. Primary CNS lymphoma
CMV encephalitis

- 39y old diagnosed 2004
- Not seen clinic for many years
  - No HAART
  - Rapid dementing / encephalopathy illness
  - CD4 14, viral load 2 million
- Admitted:
  - CSF CMV-PCR +ve
- Prognosis poor
CMV encephalitis

- Rapid and progressive disorientation, withdrawal, apathy, cranial nerve palsies, and nystagmus
- MR:
  - Bilateral, periventricular enhancement on contrast enhanced T1-weighted scans,
  - Ventricular enlargement,
  - Diffuse white matter change, and subependymal and cortical enhancing lesions
  - May be normal and often non-specific
- CSF:
  - Usually cellular
  - Positive CMV PCR
CMV Polyradiculitis

• 30y old man diagnosed 2000 - CD4 36

• Presentation:
  – Progressive balance problems
  – Unable to bend over without fall over
  – Abnormal gait
  – Difficulty climbing the stairs
  – Bladder / bowel function normal

• Examination:
  – Reduced tone both legs; Reflexes reduced knee/absent ankle
  – Power 4/5 knee and ankle symmetrically
  – Sensation absent:L4-S1
CMV polyradiculitis

• Presentation:
  – Rapidly progressive, painful, bilateral ascending flaccid paralysis
  – Areflexia
  – Saddle anaesthesia
  – Sphincter dysfunction and urinary retention.

• MR
  – Diffuse enhancement of cord parenchyma, nerve roots and meninges

• CSF - PMN pleocytosis and PCR +ve.

• NCS - Axonal neuropathy.
OI’s in the lungs
Patient 4

• A 22yr old African man presents with a 10 day history of profound breathlessness, dry cough and fever in December
• Auscultation is unremarkable.
• Investigations:
  • Rapid HIV Ab +ve
  • Saturation 89% on air
  • pO2 7.6 kPa, pCO2 3.9kPa
  • CXR as shown
• **Clinical diagnosis PCP**
Challenges

A. Confirmatory diagnosis
B. 2\textsuperscript{nd} line therapy for severe disease
C. CMV co-infection
D. PCP IRS
E. DPHS mutations
A. Confirmatory diagnosis

- Confirmation - PCR or histochemical/fluorescent stains
- Yield: Induced sputum (50-90%), BAL (90-95%), trans-bronchial biopsy (>90-95%)
Patient 4

- High dose IV co-trimoxazole and steroids are commenced
- Subsequent BAL is positive for pneumocystis and CMV on staining.

- Over the next 4 days he deteriorates and is intubated and ventilated

- At 7 days there is no progress
Patient 4

Day 1 - Day 4
Which alteration to his therapy would be most appropriate?

- Add ganciclovir
- Switch/add caspofungin
- Change/add pentamidine
- Switch to clindamycin/primaquine
- Start dapsone/trimethoprim
- Add trimetrexate
PCP - treatment

- 2nd line:
  - Clindamycin and primaquine (mild to severe)
    - AE: metHB (< with 15mg primaquine), rash
  - Pentamidine (severe)
    - AE: nephrotoxicity, hypotension, hypoglycaemia
  - Trimetrexate (severe)
  - Caspofungin
  - Trimethoprim and dapsone (mild to moderate)
  - Atovaquone (mild)
  - Consider overlap for 48hrs where not toxicity

- HAART commencement/optimisation
C. CMV co-infection

- N=84
- Cohort analysis
- No difference on 21d mortality
- Significant difference at 6m
When would you start HAART?

- Immediately
- After 1-2 week when stable
- When switching to prophylaxis
- At OPD follow-up
- At 3 months
D. When to start ART: ACTG 5164: Immediate vs. deferred in patients with acute OIs (not TB)

- Immediate treatment group had reduced rate of AIDS progression or death (14.2%) compared with deferred treatment group (24.1%)
- No differences in IRIS between arms (10 immediate vs. 13 deferred)
  - However, 70% of patients with PCP received corticosteroids

- The most common OIs were PCP (63%), Cryptococcus (12%), BI (bacterial infection (11%)), TB excluded

Adapted from Zolopa A, et al. CROI 2008, Boston, MA, USA, Abstract 142
E. DHPS mutations and COT resistance

• What about PJP cotrimoxazole resistance?
  – DHPS mutations associated with past prophylaxis
  – Frequency falling as less COT prophylaxis
  – Variable evidence associated with failure of prophylaxis and worse outcome
Clinical challenge is diagnosis of Disseminated OIs.
Patient 5

- On admission:
- Chronic diarrhoea
- Weight loss (>1 stone)
- Examination:
  - Wasted, dehydrated
  - 38°C, tachycardia
- Standard laboratory tests unremarkable
- USS abdomen – normal
- Stool: non-typhi Group D salmonella isolated
Investigations

• BAL:
  – Negative for PCP, AFB, Gram
  – Negative for standard bacterial culture
  – Yeasts identified on initial Gram and presumed to be Candida colonisation
  – No evidence of pulmonary KS

• Ear lesion noted

• Treated as PCP
  – Started co-trimoxazole
What is your diagnosis?

- PCP
- Miliary TB
- Influenza pneumonitis
- Cryptococcal pneumonia
- Penicillium
- Histoplasma
Investigations

• Biopsy ear:
  – Penicillium marneffei
  – blood, throat swab, ear swab, and BAL all +ve

• Treatment:
  – Liposomal amphotericin (4mg/kg/day)
  – Co-trimoxazole prophylaxis
Penicillium marneffei

<table>
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<tr>
<th>Specimen</th>
<th>Isolation rate</th>
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<tr>
<td>Bone marrow</td>
<td>100</td>
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<tr>
<td>Skin lesion</td>
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<td>Blood</td>
<td>76</td>
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<td>Sputum</td>
<td>34</td>
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<tr>
<td>Lymph node</td>
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<td>Liver</td>
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<table>
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<tr>
<td>Weight loss</td>
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<tr>
<td>Skin lesions</td>
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<tr>
<td>Generalised LN</td>
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<tr>
<td>Hepatomegaly</td>
<td>51</td>
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<tr>
<td>Cough</td>
<td>49</td>
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<tr>
<td>Diarrhoea</td>
<td>23</td>
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<tr>
<td>Treatment</td>
<td>Amphotericin B (0.6-1g/day) for 2 weeks (± 5 FC), then Itraconazole 200mg BD for 10 weeks (consider IV Itraconazole if severe)</td>
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<tr>
<td>------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
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<tr>
<td>Maintenance</td>
<td>Itraconazole 200mg OD</td>
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</table>
Patient 6

- 29y abdominal Asian: presented with seizures and localising signs
- Background of weight loss, dry cough and fever for 12w
- HIV confirmed: CD4 3, Viral load 292000 – treated as TP
Oral lesions noted

- Biopsy: budding yeasts
- Culture – histoplasma capsulatum
- Treatment AMP-B
- Response good
IRS can occur
Patient 7

- Presented with PCP
  - ITU and bilateral pneumothoraces
  - CD4 2, VL >1million
- Retina
  - CMV retinitis
- Sputum
  - Aspergillus
- Blood/sputum
  - MAI
Slow but steady response

• OI treatment:
  – PCP: COT/steroids
  – CMV: ganciclovir
  – Aspergillus: Voriconazole
  – MAI: azithromycin, ethambutol, moxifloxacin, linezolid

• HIV treatment:
  – Raltegravir, Truvada
Outline

• Differing knowledge and differing requirements...

• Today I will break it down:
  • Review of many of the OI’s
  • Focus on the main clinical challenges
  • Present recent data

• Hopefully you interrupted!
Thanks
Patient 3

- 42y old man, partner diagnosed HIV+ve so has test also +ve
- Asymptomatic, CD4 46
- Starts HAART with EFV/ABC/3TC
- 2w CNS s/e attributed to EFV
- 8w later bizarre behaviour
- Diminished cognitive function, withdrawn affect. No obvious localising signs
- CT scan
Patient 3

- 42y old man, partner diagnosed HIV+ve so has test also +ve
- Asymptomatic, CD4 46
- Starts HAART with EFV/ABC/3TC
- 2w CNS s/e attributed to EFV
- 8w later bizarre behaviour
- Diminished cognitive function, withdrawn affect. No obvious localising signs
- MR scan
- **CSF:**
  - no cells, normal protein & glucose ratio
  - RPR and India ink –ve
  - JC strongly +ve
What are the challenges

A. Diagnosis
B. Place of brain biopsy?
C. Treatment
D. Research
## A. Diagnosis - Imaging

### MR FEATURES

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<th>PML</th>
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<tr>
<td>Number</td>
<td>Single-multiple</td>
<td>Usually multiple</td>
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<tr>
<td>Enhancement</td>
<td>Nil</td>
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<tr>
<td>Oedema</td>
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<tr>
<td>Location</td>
<td>Occipitoparietal</td>
<td>Basal ganglia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brain stem</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cortical</td>
</tr>
<tr>
<td></td>
<td>White matter</td>
<td>Interface grey-white matter</td>
</tr>
<tr>
<td>MR T1</td>
<td>Low signal</td>
<td>Low signal</td>
</tr>
<tr>
<td>MR T2</td>
<td>High signal</td>
<td>High signal</td>
</tr>
</tbody>
</table>
Diagnosis - CSF

• The presence of JC virus found in CSF by PCR technique
  – Sensitivity of >90% (<60% if on HAART)
  – Specificity of 96 to 98 %

• No help in blood
  – JC PCR in blood in 30 to 40 % of normal population
B. Place of brain biopsy?

• Brain biopsy has been the accepted diagnostic method
• However, typical NMR scan + JC PCR positive on CSF is highly specific and is now accepted
• **Consider if:**
  – PCR negative
  – Multiple areas or atypical appearance
  – High CD4 or on established HAART
  – PCR positive with atypical NMR
  – Confirmed other CNS diagnosis
C. Treatment

• 1\textsuperscript{st} line:
  – HAART
  – Cidofovir no benefit

• IRS:
  – Well described
  – Most often on ‘unmasking’ when worse prognosis
D. Continued research – mefloquine ineffective

RCT
SOC vs. MF
Thank you

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