Opportunistic Infections
(Prevention, Diagnosis, and Management)

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Learning Objectives
Upon completion of this presentation, learners should be better able to:

• Review the epidemiology of opportunistic infections in the era of HAART.
• Identify the most common opportunistic Infections, including diagnosis, prevention, and treatment
Faculty and Planning Committee Disclosures

Please consult your program book.

Off-Label Disclosure

There will be no off-label/investigational uses discussed in this presentation.
Case 1

- 34 year old male presents with fever, headache, dry cough, 20 pound weight loss, progressive DOE over the last 3 weeks.
- Never tested for HIV
- No past medical history
- He works as a travel agent.
- No Etoh/IDU/crack use
- Sexually active with men
- History of Gonococcal urethritis 6 years ago (treated)
Case 1, continued

Exam

T-101 F  HR-92  BP-120/70  RR-22
HEENT – PERRLA, EOMI, oral thrush
Neck – supple, No cervical lymphadenopathy
Lungs – few crackles at bases bilaterally
Heart – S1S2 no murmur, rubs, gallops
Abdominal – soft, non-tender, no hepatosplenomegaly
Extremities – no clubbing, cyanosis, edema
Neuro – non-focal
Case 1, continued
Lab Studies

- Pulse oximetry – 95% (2 liters of oxygen)
- ABG: 7.45/36/68 95%
- CBC: wbc 3.2 H/H 12.9/37 plt 150K
- Electrolytes: normal; creatinine 1.2
- CXR: bilateral interstitial infiltrates
Case 1, continued
Differential Diagnosis

• Pneumonia – atypical
  – Mycoplasma
  – Viral
  – Fungal
  – Pneumocystis
• Tuberculosis
• Congestive heart failure
• Interstitial lung disease/pulmonary fibrosis
• Malignancy
Case

- 4\textsuperscript{th} generation HIV test Positive Ag/AB
  - Reactive on multispot for HIV-1
- CD4 count- 30 cells/mm\textsuperscript{3}
- Viral Load-250,000 copies/ml
- Bronchoscopy performed and the silver stain is positive for PCP
Incidences of first AIDS-defining opportunistic infection, according to year, among all patients in care, HIV Outpatient Study, 1994–2007 (Centers for Disease Control and Prevention, unpublished data; courtesy of R. Baker and K. Buchacz).

Gardner Stage of Engagement in HIV Care
The Dismal Cascade or Continuum of Care

Gardner. CID 2011; 52:793.
Typical Relationship of Clinical Manifestations to CD4 Count in HIV Infected Patients

- Lymphoma
- Tuberculosis
- Kaposi Sarcoma
- Herpes Zoster
- Pneumocystis
- Mucosal Candidiasis
- Cryptococcosis
- Mucosal Herpes Simplex
- Toxoplasmosis
- CMV
- MAC
- Cryptosporidiosis

Source: Expert Opinion

ACTHIV 2015: A State-of-the-Science Conference for Frontline Health Professionals
Pneumocystis jiroveci pneumonia - PCP

- Most common Opportunistic infection (OI) in the USA
- Formerly P. carinii
- CD4 < 200 (prophylaxis)
- Subacute progressive sx: dry cough, SOB, exertional dyspnea, fevers, night sweats, weight loss
- Dx: demonstration of organism on silver stain – usually obtained via broncho-alveolar lavage
Treatment
Moderate-Severe

• First line Therapies (21 days)
  – High dose TMP-SMX (15-20mg/kg/day given q6 or 8h IV, may switch to po after clinical improvement
  – Corticosteroids (PaO2 <70mmHg or AA>35)

• Alternative Therapies
  – Pentamadine 4mg/kg IV daily
  – Primaquine 30mg po once daily + clindamycin IV 600mg q6h or 900mg q8h

Source: http://aidsinfo.nih.gov/guidelines
Treatment
Mild to moderate

• First line Therapies (21 days)
  – TMP-SMX (TMP 15-20mg/kg) given po in 3 divided doses
  – TMP-SMX DS 2 tablets TID

• Alternative Therapies
  -Dapsone 100mg daily +TMP 15mg/kg/day po (3 divided doses)
  -Primaquine 30mg po daily + clindamycin po (300mg po q6h or 450mg q8h)
  -Atavoquone 750mg BID with food

Source: http://aidsinfo.nih.gov/guidelines
### Steroid Dosing Schedule

<table>
<thead>
<tr>
<th>Days</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1-5</td>
<td>Prednisone 40mg po bid</td>
</tr>
<tr>
<td>Days 6-10</td>
<td>Prednisone 40mg po Daily</td>
</tr>
<tr>
<td>Days 11-21</td>
<td>Prednisone 20mg po Daily</td>
</tr>
</tbody>
</table>

IV Methylprednisolone can be given as 75% of the prednisone dose

Source: http://aidsinfo.nih.gov/guidelines
While on rounds, the resident ask you if you should start antiretroviral therapy on this patient?

A. Treat the OI first and start HAART within 2 weeks.
B. Defer HAART until the patient has been established in the office.
C. Call Dr. Squires for a phone consult.
D. Not sure.
Immediate vs. deferred ART in the setting of Acute OI: ACTG 5164

- Randomized Phase IV strategy trial in US, South Africa
- Determine the optimal timing of ART in the setting of an acute OI or serious bacterial illness
- Comparison of immediate (2 weeks) vs. delayed (45 days) ART
- Included confirmed or probable diagnoses of OIs and bacterial infections for which antimicrobial therapy are available

ACTG 5164: Immediate vs. Delayed ART with an Acute OI

• 228 pts with a treatable OI
  • Most common OI: PCP (63%)
  • TB excluded
  • Small number cryptococcal meningitis, Toxoplasmosis

• AIDS progression/death: immediate rx (14%) vs. delayed rx (24%)

• No difference in safety/toxicity, IRIS, or week 48 responses

ACTG 5164 summary and recommendations

• Immediate ART compared to deferred
  – Results in less AIDS progression or death
  – More rapid CD4 cell increase
  – Equivalent virological response by 48 weeks
  – Requires somewhat more ART changes
  – No difference in safety
  – No difference in IRIS

• TB was not included. Small numbers of Cryptococcal meningitis, Toxoplasmosis

Immune Reconstitution Inflammatory Syndrome (IRIS)

- Improved Cell Mediated Immunity with restoration of both memory and naïve CD4 cells
- Increased CD4/CD8 cells detect hidden pathogens which were ignored with deficiency of immunity previously
- Result in inflammatory process at the area of occult / sub-clinical infections
- Usually improves with control of inflammation and specific treatment
# Immune Reconstitution Inflammation Syndrome (IRIS)

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>CLINICAL PRESENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAC</td>
<td>Local adenitis</td>
</tr>
<tr>
<td>mTB</td>
<td>Paradoxical reactions</td>
</tr>
<tr>
<td>CMV</td>
<td>Atypical retinitis; uveitis</td>
</tr>
<tr>
<td>VZV</td>
<td>Dermatomal zoster</td>
</tr>
<tr>
<td>HSV</td>
<td>Atypical HSV; HSV encephalitis</td>
</tr>
<tr>
<td>HCV &amp; HBV</td>
<td>Hepatitis flare; ?IRD vs HAART toxicity</td>
</tr>
<tr>
<td>JC VIRUS (PML)</td>
<td>Inflammatory PML</td>
</tr>
<tr>
<td>KAPOSI’S SARCOMA</td>
<td>New lesions in new sites (LN); flares of existing lesions</td>
</tr>
</tbody>
</table>

Other...

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French, Barcelena 202, M1OrB106; French, HIV Medicine 2000;1:107
Onset of IRIS

Fig. 1. Time to diagnosis of IRIS after starting HAART. IRIS, immune reconstitution inflammatory syndrome; HAART, highly active antiretroviral therapy.

Source: AIDS 2005, Vol 19 No4; 399-406, Samuel A. Shelburne et al
Case

- You order a genotype
- You start the patient on Emtricitabine/Tenofovir and Darunavir boosted with Ritonavir while the patient is in the hospital
- He returns to your office 1 week after discharge and is feeling much better
Question 2

• As part of his examination, he has a dilated retinal examination and you see this:
What is your recommendation?

A. Start Ganciclovir
B. Suggest intraocular Ganciclovir implant
C. Start Acyclovir
D. Continue present treatment with HAART
E. Something else
Question 2

• As part of his examination, he has a dilated retinal examination and you see this:
CMV Retinitis
Case 2

- RL is a 40 year old male with long standing HIV
- He has been non-compliant with his HAART regimen
- He tried a few regimens but falls out of care soon after starting
- His last CD4 count 1 year ago was 10 cells/mm$^3$ and his Viral load was 350,000 copies/ml
Case 2

- He presents with weight loss, headache, fever
- He has a spinal tap which shows:
  - WBC: 2
  - 100% lymphocytes
  - Mildly elevated protein
- CSF Cryptococcal Antigen is positive 1: 128
Cryptococcal Meningitis in Patients with HIV Infection

- Epidemiology: CD4 count < 50 cells/mm3 (75% cases)

- Diagnosis
  - CSF: Ag positive 95-100%
  - Serum: Cryptococcal antigen positive 95-99%
  - Blood Culture: positive 75%

- Poor prognosis
  - Abnormal mental status at presentation
  - Low CSF WBC
  - High Cryptococcal antigen > 1: 1024

- Beware of unusual presentations
  - Skin (molluscum)
  - Lung (variable x-ray)
  - Screening with Cryptococcal antigen: Titer > 1:8 should be treated
ACTHIV 2015: A State-of-the-Science Conference for Frontline Health Professionals
Therapy of Cryptococcal Meningitis

Induction, Consolidation, and Maintenance

- **2 weeks**
  - Liposomal amphotericin B 3-4 mg/kg IV daily qd
    + Flucytosine 25mg/kg daily
    +/-
  - Daily LP if CSF pressure elevated

- **8 weeks**
  - Fluconazole 400 mg po daily

- **At least one year**
  - Fluconazole 200 mg po

Source: http://aidsinfo.nih.gov/guidelines
Management of increased ICP

- For pts with ICP > 250 mm H₂O-- perform daily or every other day LPs. Remove CSF volume 20-30 cc to reduce Opening pressure to 50% of the baseline.
- Placement of lumbar drain and option, but infections and drain malfunction are major concerns.
- Ventriculostomy catheter to drain and monitor ICP. High risk for infection.
- Ventriculoperitoneal (internalized) shunt in pts with or without evidence of hydrocephalus. Risks include potential infection, dissemination of *cryptococcus*, and shunt obstruction.

Source: http://aidsinfo.nih.gov/guidelines
## Increased Intracranial Pressure (ICP)

### Association of Mortality with Baseline CSF Opening Pressure

<table>
<thead>
<tr>
<th>Opening Pressure</th>
<th>&lt;190 – 249 mm n = 102</th>
<th>250 – 349 mm n = 59</th>
<th>&gt; 350 mm n = 60</th>
</tr>
</thead>
<tbody>
<tr>
<td># (%) of Deaths</td>
<td>21 (21%)</td>
<td>16 (27%)</td>
<td>23 (38%)</td>
</tr>
<tr>
<td>Median mos. To death</td>
<td>10.5</td>
<td>7</td>
<td>6◊</td>
</tr>
</tbody>
</table>

◊ Pts with the highest baseline Ops (>250) also had higher titers Cryptococcal antigens and more frequent H/A, meningismus, papilledema, hearing loss and pathologic reflexes

Serial Crypt Antigen Titers

- **Serum**
  - Changes do NOT correlate with therapeutic response

- **CSF**
  - Changes are helpful but repeated LPs not necessary if patient is responding well clinically

- **Note:**
  - Some clinicians advocate LP with culture and Ag before stopping maintenance: controversial

Source: http://aidsinfo.nih.gov/guidelines
Considerations in Starting ART during an Acute Opportunistic Infection

<table>
<thead>
<tr>
<th>Opportunistic Infection</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCP</td>
<td>Art should be initiated within 2 weeks of diagnosis of PCP.</td>
</tr>
<tr>
<td>Esophagitis (candida)</td>
<td>No data.</td>
</tr>
<tr>
<td>Disseminated mycobacterial infection</td>
<td>ART should be started as soon as possible after the first 2 weeks of starting MAC therapy.</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>No data: Most physicians would initiate ART within 2-3 weeks after a diagnosis of Toxoplasmosis.</td>
</tr>
<tr>
<td>Progressive multifocal leukoencephalopathy</td>
<td>Art should be initiated as soon as possible.</td>
</tr>
<tr>
<td>Cryptococcal Meningitis</td>
<td>Controversial</td>
</tr>
</tbody>
</table>

Source: http://aidsinfo.nih.gov/guidelines
# Criteria for Starting, Discontinuing, and Restarting Opportunistic Infection Prophylaxis for Adults with HIV

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<tbody>
<tr>
<td><strong>OI</strong></td>
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<tr>
<td><strong>PCP</strong></td>
<td>CD4 &lt; 200 or oral candidiasis</td>
<td>CD4 &gt; 200 for 3 mos</td>
<td>CD4 &lt; 200</td>
<td>Prior PCP</td>
<td>CD4 &gt; 200 for 3 mos as a result of ART</td>
<td>CD4 &lt; 200</td>
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<tr>
<td>Toxoplasmosis</td>
<td>+ serum IgG</td>
<td>CD4 &gt; 200 for 3 mos</td>
<td>CD4 &lt; 100 – 200</td>
<td>Prior toxoplasmic encephalitis</td>
<td>CD4 &gt; 200 sustained on ART for &gt; 6 months and completed initial therapy and is asymptomatic</td>
<td>CD4 &lt; 200</td>
</tr>
<tr>
<td></td>
<td>CD4 &lt; 100</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>MAC</strong></td>
<td>CD4 &lt; 50</td>
<td>CD4 &gt; 100 for 3 mos</td>
<td>CD &lt; 50 – 100</td>
<td>Documented disseminated disease</td>
<td>CD4 &gt; 100 sustained and completed 12 mos of MAC tx and asymptomatic</td>
<td>CD4 &lt; 100</td>
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<tr>
<td>Cryptococcosis</td>
<td>none</td>
<td>n/a</td>
<td>n/a</td>
<td>Documented disease</td>
<td>CD4 &gt; 100 sustained and completed initial therapy and asymptomatic</td>
<td>CD4 &lt; 100</td>
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<tr>
<td>Histoplasmosis</td>
<td>CD4&lt;150 for those at risk</td>
<td>CD4&gt;150 for 6 months on ART</td>
<td>CD4&lt;150</td>
<td>Documented disease</td>
<td>&gt; 1year of Tx, negative fungal blood cx, Cd4 &gt;150, and ART for 6 months</td>
<td>CD4&lt;150</td>
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<tr>
<td>CMV</td>
<td>none</td>
<td>n/a</td>
<td>n/a</td>
<td>Documented end-organ disease</td>
<td>CD4 &gt; 100 sustained (3-6 months) in response to ART and no evidence of active disease and regular exams</td>
<td>CD4 &lt; 100</td>
</tr>
</tbody>
</table>

*Source: [http://aidsinfo.nih.gov/guidelines](http://aidsinfo.nih.gov/guidelines)*
Summary:

• Opportunistic Infections are still seen in the HAART era and require clinicians to have an understanding of their pathogenesis, clinical presentation, and treatment.

• Guidelines are changing with regards to starting ART during an acute opportunistic infection.

• Remember prophylaxis!!