ACTHIV 2017: A State-of-the-Science Conference for Frontline Health Professionals
Opportunistic Infections
4 Things You Need To Know

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Objectives

• Identify and manage common OIs in the HIV-infected patients

• Identify and manage Immune Reconstitution Inflammatory Syndrome (IRIS)
Off Label Disclosures

• None
Key Fact #1: CD4 count correlates with risk of specific OIs in untreated HIV disease
CD4 count correlates with risk of specific OI’s in untreated HIV disease

Adapted from Bartlett JG, Galant JE, Pham PA. Medical Management of HIV. 2012
Case #1

44 y/o M with HIV (CD4 94, not on ARVs or prophylaxis) presents with 1 month of progressive SOB, non-productive cough, fevers, night sweats, and weight loss.

- Exam: Afebrile, 90% RA. Diffuse crackles, thrush, bilaterally and mild wheezing.

- Labs: WBC 8.3. LDH 386, BDG>500.

- ABG: 7.44/35/59 on RA
Case #1: continued
ARS: Which of the following is NOT true

A. He should be started on empiric treatment for community acquired pneumonia, TMP/SMX, and prednisone

B. If this patient has a septra allergy you should consider septra desensitization

C. Pneumocystis carinii causes pneumonia in rats

D. The specificity of beta d-glucan with PCP is 92%
When to suspect PCP

• Subacute presentation of cough: often present with dry cough, DOE
  • Hypoxemia with normal CXR (possible in early disease)
  • Desaturation with exertion

• CD4 <200
  • >90% of cases occur with CD4<200

• CXR and chest imaging-
  • Diffuse bilateral symmetric infiltrates, seen in 60% of cases
  • HRCT for ground glass (Sensitivity ~100%, specificity 89%)
  • Pneumothorax common, 35% in cystic PCP
  • Lymphadenopathy, cavitations and effusion are NOT common
PCP: Laboratory Diagnostics

• No culture system for *P. jirovecii*

• Sensitivity of stained respiratory secretions
  • Induced sputum: <50-90%
  • BAL: 95-100%

• Elevated LDH
  • Sensitivity 83-100%, specificity 25-85%

• Beta D Glucan
  • (1→3)-β-D-glucan is a component of the cell wall of most fungi (including *P. jirovecii*)
  • Sensitivity 92%, specificity 65% for PCP using a cutoff of 80 pg/ml
  • Median level in PCP was 408
  • Other fungal causes of positive BDG: candidiasis, histo, cryptococcus
  • Most useful if negative

PCP Treatment

- **TMP-SMX is first-line therapy**
  - Dosing:
    - TMP/SMX (TMP 15–20 mg/kg and SMX 75-100mg)/kg/day divided q6h-q8h
    - Use IV TMP/SMX for moderate to severe disease and may switch to PO after clinical improvement
    - Patients who get PCP despite TMP-SMX prophylaxis still respond to standard dosing
  - Desensitization protocols available for patients with allergy

- **Steroids within 72 hours in severe disease: RA PaO₂<70 mm Hg or A-a gradient>35 mm Hg**
  - Prednisone 40 mg bid x 5d then
  - Prednisone 40 mg qd x 5d then
  - Prednisone 20 mg qd x 11d

- **Duration of therapy: 21 days then start secondary prophylaxis**

- **Adverse effects are common in HIV+ patients**
  - Rash, fever, leukopenia, thrombocytopenia, azotemia, hepatitis, hyperkalemia
  - Try to “treat through” common (non-life threatening) reactions if possible

DHHS OI Guidelines 2016
Alternative Rx for Failure or Toxicity

**Moderate to severe disease (PaO2 < 70, A-a grad > 35):**

- **Pentamidine (IV) 4 mg/kg IV daily**
  - Historically preferred as the 2nd line agent for severe disease (A-a gradient > 45) because of more efficacy data
  - Serious side effects (irreversible renal and pancreatic islet cell toxicity, orthostatic hypotension, profound hypoglycemia, cytopenias)

- **Clindamycin (IV: 600mg Q6h or 900mg Q8h. PO: 450mg Q8h) + Primaquine (30mg PO daily; check G6PD)**

**Mild disease (PaO2 > 70, A-a grad < 35):**

- **Clindamycin (450 mg q6hr or 600mg q8hr) + primaquine 30mg (base) PO daily**
- **Atovaquone 750mg PO BID with food**
- **Dapsone 100mg PO daily + TMP 15mg/kg/day PO [3 divided doses]**

DHHS OI Guidelines 2016
Back to Case 1

- Started on empiric CTX/doxy + TMP-SMX/prednisone.

- Could not get induced sputum.

- BAL:
  - AFB smear and cx neg
  - Bacterial: oral flora
  - PCP positive

- After BAL returned: CTX/doxy stopped, TMP-SMX/prednisone continued.
Case #2

37 y/o M with HIV (CD4 28) presents with fever, AMS, and seizure.

ARS #2: What do you recommend?

A. Brain biopsy
B. Start empiric toxoplasmosis therapy
C. Start RIPE to treat empirically for TB
Selected Ddx of CNS Space Occupying Lesions in AIDS

**Short Differential**

- Toxoplasma gondii
- Primary CNS lymphoma

**Long Differential**

**Bacterial**
- Pyogenic abscess
- Nocardia
- Rhodacoccus
- Tuberculoma/NTM
- Syphilis

**Fungal**
- Cryptococcoma
- Histoplasma

**Parasitic**
- Toxoplasma gondii
- Chagas disease/chagoma

**Malignancy**
- Primary CNS lymphoma

Skiest DJ Focal Neurologic Disease In patients with acquired immunodeficiency syndrome. CID 2002.
Toxoplasma Encephalitis: Epi and Clinical

• Occurs at CD4<100, but highest risk if CD<50

• Almost exclusively due to reactivation of latent infection

• Transmission occurs by ingesting oocysts excreted in cat feces (in cat litter or soil) or by ingesting undercooked meat (pork and lamb) or raw shellfish containing tissue cysts

• Subacute presentation over several weeks: HA, fever, behavioral changes, confusion, hemiparesis, seizures, ataxia, CN palsies, diffuse encephalitis.

Skiest, CID 2002.
CNS Toxoplasmosis: Imaging

- Lesions are most commonly located in the parietal or frontal lobes and at the corticomedullary junction, basal ganglia, thalamus, and pituitary gland.

- Lesions can be single or multiple:
  - Classic finding is ≥2 ring-enhancing lesions with surrounding edema
  - But up to 27%–43% of patients have a single lesion

- In rare cases patients can have diffuse encephalitis with no focal lesions
CNS Toxoplasmosis: Laboratory Diagnosis

• **Serum toxo IgG:** if negative then virtually excludes infection because <3%–6% of patients with TE have negative IgG

• **CSF studies:**
  • Chemistries may be normal or show mild increase in protein, lymphocytic pleocytosis, low glucose
  • Toxo CSF PCR: sensitivity only 50% although specificity 96-100%. A negative test does not rule out disease.

• It is very difficult to distinguish between Toxo and primary CNS lymphoma based on clinical findings alone

Skiest, CID 2002.
CNS Toxoplasmosis: Treatment

• Usually treat empirically based on positive serum IgG
  • Follow MRI in 2 weeks
  • **Should see radiographic improvement within 2 weeks** – if not then consider alternative diagnosis, pursue biopsy to rule out other causes

• **First choice regimen:** Pyrimethamine plus sulfadiazine plus leucovorin x 6 weeks
  • Then secondary ppx: pyrimethamine plus sulfadiazine plus leucovorin
  • **Pyrimethamine:** rash, nausea, and bone marrow suppression (can reverse by increasing leucovorin dose)
  • **Sulfadiazine:** rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhea, and crystalluria (encourage hydration)

• **Alternative regimen (for toxicity or clinical failure)**
  • Pyrimethamine plus clindamycin
  • **Pyrimethamine free:** TMP/SMX alone or Atovaquone+-sulfadiazine
  • Other possible regimens listed in CDC guidelines, especially if need IV options

• **Avoid steroids (if possible) if treating empirically because this will treat lymphoma as well**

DHHS OI Guidelines 2016
Primary CNS Lymphoma

- Occurs usually at CD4<50, subacute presentation

- Imaging:
  - Lesions can be single or multifocal, or often single
  - Usually enhance homogenously, but can also be rim-enhancing
  - Located in the cerebrum, basal ganglia, cerebellum, brainstem
  - Characteristic finding is to be next to CSF (eg periventricular, meningeal, subependymal)

- CSF findings:
  - Mild elevated protein and pleocytosis
  - EBV PCR: sensitivity >80%, specificity 94-100%
Case #3

• CC: 51 M p/w shortness of breath

• HPI:
  • Dyspnea & reduced exercise tolerance x 1 mo
  • Sweats, fevers, 10 lb weight loss x 1-2 mo
Labs / Studies at presentation

- HIV Antibody (+), CD4 39
- Sputum AFB smears (-) x 3
  
  Serum CrAg (+) 1:32,768

  LP: OP 26 cm, WBC 2 (N0, L93, M7), RBC 2, Glu 47, Prot 42
  
  CSF CrAg 1:128,
  
  CSF cx C neoformans

  Induced sputum + BAL
  
  C neoformans

  Blood cx
  
  C neoformans
Cryptococcus Meningitis

- Most cases occur when CD4<100

- Clinical:
  - Presents as subacute meningitis or meningoencephalitis
  - Can also see encephalopathic signs/sx due to elevated ICP

- Diagnosis:
  - Serum and CSF CrAg are almost always positive
  - CSF studies: lymphocytic pleocytosis or no cells, mildly elevated protein, glucose normal to low, elevated OP
  - Low CSF WBC portends a poorer prognosis
Cryptococcal Meningitis: Treatment

- **Induction (14 days):**
  - Amphotericin 0.7 mg/kg/d or liposomal amphotericin 3-4 mg/kg/d plus
  - Flucytosine (5-FC) 100mg/kg/d in 4 divided doses

- **Consolidation therapy (8 weeks):**
  - Fluconazole 400mg (6mg/kg) PO daily

- **Chronic maintenance therapy:**
  - Fluconazole 200mg PO daily
  - Consider stopping when CD4>200 and VL suppressed for 6 mo

Cryptococcal Meningitis: Management of Elevated ICP

- Elevated ICP is the leading cause of death from CM in the first 2 wks after diagnosis

- Management strategy:
  - Measure OP at diagnosis. If OP is elevated and pt has sx: daily LPs to remove volume (~20-30cc) in order to bring the OP down to normal or by 50% if very high
  - Aim for at least 2 days of stable pressures
  - If symptoms persist or can’t do daily LPs, then consider EVD/lumbar drain
  - VP shunt can be done in the setting of anti-fungals if other measures fail

Case #3 continued

ARS #3: When do you start antiretroviral therapy?

A. Within 2 weeks

B. 5 weeks from start of anti-fungal therapy

C. 8 weeks from start of anti-fungal therapy
Starting ARVs during an Acute OI

**Advantages**
- Sometimes ARVs are the best treatment for the OI
  - PML, cryptosporidiosis, KS, microsporidiosis
- Prevention of a second OI
- Restore pathogen-specific immunity (more rapid clearance of OI)
- Slow HIV progression

**Disadvantages**
- Risk of IRIS (especially if occurs in CNS)
ART Timing in Cryptococcal Meningitis
COAT Study, 2013 (trial halted)

<table>
<thead>
<tr>
<th>Cryptococcal Optimal ART Timing (COAT) Study RCT (UG+S.Af.), 2013 (Boulware, CROI Atlanta, 3/6/13)</th>
<th>Early ART (n=88)</th>
<th>Later ART (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampho/Fluc800 2w, then Fluc800 until CSF sterile, then Fluc 400 x 8wks</td>
<td>PLAN: &lt;48h → 7d (5-10)</td>
<td>PLAN: &gt;4 wks → 32d (28-36)</td>
</tr>
<tr>
<td>Median CD4+ count</td>
<td>19/uL (9-69)</td>
<td>28/uL (11-76)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>45% death by 6 mo.</td>
<td>30% death by 6 mo.</td>
</tr>
<tr>
<td>CSF WBC &lt; 5 cells/mm³</td>
<td>HR 2.21 (0.91-5.34)</td>
<td>ref</td>
</tr>
<tr>
<td>CCM-IRIS (definite/probable/possible)</td>
<td>16.2%</td>
<td>10.1%</td>
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</table>

Death: CSF WBC < 5 cells/mm³
HR: 2.21 (0.91-5.34) ref

Death by 6 mo.:
- 45% in Early ART group
- 30% in Later ART group

Death by 6 mo.:
- HR 2.21 (0.91-5.34) p=0.03
- HR ref (p=0.008)

CCM-IRIS:
- 16.2% in Early ART group
- 10.1% in Later ART group

p=0.347
Summary Cryptococcal Meningitis

• In general, delay ART for 4-5 weeks

• Patients with <5 CSF WBC have a higher risk of mortality and have more to gain with delayed ART.
When NOT to immediately start ART in the setting of an OI: the Zuckerberg San Francisco General Hospital Experience

• **CMV retinitis:** We wait 14 days. Limited data.

• **Inflammatory CNS lesion:** For those who have evidence of brain edema, mass effect, or neurologic deficit we recommend waiting at least 14 days of OI antimicrobial therapy. There is no available relevant evidence.

• **Cryptococcal Meningitis**

W86 clinical guidelines: http://hivinsite.ucsf.edu/InSite?page=md-ward86-art-oi
Key Fact #2: OIs can be prevented with ART and primary prophylaxis
# Primary Prophylaxis of OIs: The Basics

<table>
<thead>
<tr>
<th>OI</th>
<th>Indications for Primary ppx</th>
<th>Regimen of Choice</th>
<th>Alternative Regimens</th>
<th>When to stop ppx</th>
</tr>
</thead>
</table>
| PCP                 | CD4<200 or CD4<12% or h/o thrush or AIDS defining illness                                  | TMP-SMX 1 DS daily or 1 SS         | • TMP-SMX 1 SS daily or 1 DS tiw  
• Dapsone (check G6PD)  
• Dapsone + pyrimethamine + leucovorin  
• Aerosolized pentamidine  
• Atovaquone                                                           | CD4>200 for >3 mo, HIV RNA <40                                                             |
| Toxoplasmagondii    | Toxo IgG positive AND CD4<100                                                             | TMP-SMX 1 DS daily                 | • TMP-SMX 1 DS tiw  
• Dapsone + pyrimethamine + leucovorin  
• Atovaquone 1500 mg daily                                                | CD4>200 for >3 mo, HIV RNA<40                                                             |
| MAC                 | CD4<50 and no active MAC  
*send AFB Bcx first                                                      | Azithro 1200mg qweek                | • Azithro 600mg po twice/week  
• Rifabutin 300mg po daily (watch for drug interactions, r/o TB)      | CD4>100 for >3 mo, HIV RNA<40                                                             |

DHHS OI Guidelines 2016
Key Fact #3. Ockham’s Razor does not apply to OIs and AIDS
Case #4

40 yo M, with HIV (last CD4 420 and undetectable VL, one and half years ago, loss to follow-up) presents to urgent care with cachexia, fever, diarrhea (10x a day), and abdominal pain

• **PMH:**
  - HIV diagnosed 2 years ago, CD4 380 VL 80K.
  - Started on truvada and dolutegravir, suppressed for 6 months, but then lost to follow up

• **SH:** immigrated from Mexico 20 years ago, marginally housed

• **Labs:** Hgb 7, CD4 48 (6%), VL 200K, nl LFTs and Cr 1.0
Imaging

**Abdominal CT**

Bulky mesenteric, retroperitoneal, and portacaval lymphadenopathy. Non-dilated fluid filled loops of small bowel and colon suggestive of ileus.

**Chest CT**

Numerous pulmonary nodules UL and RML- largest 1.8cm.
Syndromic Differential Can Help Predict Pathogens in Patients with a CD4<50

**Short DDx:**
- AIDS + Fever + Wasting + LAD
  - Disseminated MAC
  - Tuberculosis
  - Disseminated Fungal (Crypto, Histo, Cocci)
  - Malignancy

**Short DDx:**
- AIDS + Pulmonary Nodules
  - Tuberculosis
  - Kaposi's Sarcoma
  - Fungal (Cryptococcus, Coccidioidomycosis)
  - Lymphoma

**Short DDx:**
- AIDS+ Chronic Diarrhea
  - Parasites (cryptosporidium, microsporidium)
  - Bacterial (salmonella, shigella), *mycobacterial* (MAC colitis, TB ileitis)
  - Viral: CMV colitis, Kaposi’s Sarcoma (HHV8)
  - Fungal: histoplasmosis
  - Other: HIV enteropathy.
Case 4 (cont.)

- Stool cultures and O&P: giardia ag positive, entamoeba histolytica, cryptosporidium.
- Serum CrAG-negative
- Urine histo Ag-negative
- Violaceous lesion on base of tongue
Colonoscopy
Colonoscopy
Cytopathic changes consistent with CMV

Nucleomegally and smudgy chromatin
Colonoscopy
Granulomatous inflammation with AFB
Lung Biopsy - Kaposi’s Sarcoma

Stains for HHV-8

H&E - spindle cells
Case 4-Final Diagnosis

1. Disseminated KS: Tongue, skin, and lungs

2. CMV esophagitis and colitis

3. Disseminated MAC – MAC on LN and colon biopsies; blood cultures grew MAC
When to suspect Mycobacterium Avium Complex

Clinical:
- Fever, weight loss, wasting, +/- diarrhea, +/- abdominal pain

Laboratory:
- CD4<50
- Elevated AlkPhos
- Often with anemia or pancytopenia due to bone marrow infiltration

Diagnostics:
- AFB Blood Cultures (important to draw prior to given azithromycin)
  - Sensitivity 91% for 1 AFB blood cultures
  - Sensitivity 98% for 2 AFB blood cultures
- CT abdomen often reveals hepatosplenomegally and intrabdominal lymphadenopathy
- May need tissue biopsy
MAC Treatment: At Least 2 Drugs

<table>
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<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>+/- Drug 3</th>
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<tbody>
<tr>
<td>Clarithro (more data)</td>
<td>Ethambutol</td>
<td>Rifabutin</td>
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<tr>
<td>Or</td>
<td></td>
<td></td>
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<tr>
<td>Azithro (better tolerated, less drug interactions)*</td>
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</tbody>
</table>

- Consider a 3rd drug when:
  - High burden of disease
  - Not on ARVs
  - **mortality benefit with 3 drugs vs. 2 drugs, but pre HAART era

- Monitoring:
  - Check AFB cx at 4-6 weeks
  - Consider treatment failure, if no improvement in sx and still bacteremic after 4-8 wks

* Dunne CID 2000
** Benson CID 2003
CMV and AIDS

• Usually occurs when CD4<50

• CMV in AIDS manifests as (in order of frequency):
  • **Retinitis**: before HAART, 30-40% developed this
    • Screening eye exams in patients with CD4 <50 recommended
  • **GI**: colitis (5-10%), esophagitis (<5-10%)
  • **Neuro**: encephalitis, polyradiculomyelopathy
  • Pneumonitis: very rare, usually bystander in BAL and not cause of pulmonary disease

Diagnostics
• CMV PCR not helpful, except for in setting of CNS involvement
• **Need tissue (aside from ocular disease)**
Key Fact #4: There is an increased risk of IRIS with CD4<50-100
5 weeks after starting ARVs, the patient was readmitted with new fever to 39.4, CT showed mild increase in size of mediastinal/intra-abdominal nodes.

**CD4 went from 46 -> 85, and VL 200 K→ 110**

What’s on your ddx?
DDx: Worsening of OI After Starting ARVs

- Immune reconstitution inflammatory syndrome (IRIS)
- Adverse med effect
- Treatment failure (noncompliance, resistance, poor absorption of meds)
- New OI, malignancy, autoimmune process
ARS #4: Which statement is **INCORRECT**?

A. NSAIDS can be used to treat mild IRIS

B. Mortality of cryptococcus IRIS is over 20%

C. This patient could have KS IRIS

D. PCP IRIS is common
What is Immune Reconstitution Inflammatory Syndrome (IRIS)?

• Broadly defined as a syndrome of an exaggerated immune response to antigens after starting ARVs
  • To persistent antigens of an OI that is being treated (paradoxical IRIS)
  • To viable pathogens that were subclinical and not being treated (unmasking IRIS)

• **Timing**: Recent initiation of ARVs (usually within 3 mo) with decrease in VL and/or increase in CD4

• Usually infections but can also be malignancy (KS-IRIS).

• Little is known about pathogenesis

## Classic IRIS Presentations

| MAC | Localized Disease (e.g., lymphadenitis, abscesses)  
     | Bacteremia absent |
|-----|--------------------------------------------------|
| Cryptococcus | Recurrence of meningitis frequently associated w/increased ICP  
            | Lymphadenitis  
            | Cryptococcomas |
| TB  | Fever, lymphadenitis, cold abscesses, worsening pulmonary disease |
| CMV | Immune recovery uveitis, can be sight threatening |
| KS  | Rapid progression of KS lesion |

- PCP IRIS has been documented, but rare

IRIS Incidence and Outcome

• Overall incidence of IRIS is ~15-30%

• ↑ risk if starting ARVs at a low CD4 (<50) or high VL (>100K)

• ~5% mortality in IRIS:
  • 3% with TB-IRIS
  • 20% with CCM-IRIS

IRIS: Treatment

• **Step 1:** Optimize or initiate treatment of the OI

• **Step 2:** Supportive and symptom-directed therapy (most cases are self-limiting). Most cases resolve in several weeks.

• **Step 3:** Consider anti-inflammatory therapies
  • NSAIDs for less severe symptoms
  • Corticosteroids most commonly used for moderate to severe disease. Often start prednisone 1mg/kg and taper based on clinical response (dose for TB IRIS).

• Don’t Stop ART!

Case #4: Follow-Up

• Likely paradoxical IRIS

• AFB blood cultures negative

• The patient was started on NSAIDS and symptoms resolved. We avoided steroids because patient had known Kaposi’s Sarcoma.

• One month later, imaging showed improvement in abdominal LAD, and pulmonary lesions.
Key References

• DHHS 2016 OI Guidelines: https://aidsinfo.nih.gov/contentfiles/lvguidelines/Adult_OI.pdf

• AIDS Education and Training Centers’ National Resource Center: www.aidsetc.org

• HIV Insite and Ward 86 Management Recommendations: http://hivinsite.ucsf.edu
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