HIV-Associated
Opportunistic Infections

Jonathan Vilasier Iralu, MD, FACP
Indian Health Service Chief Clinical Consultant for Infectious Diseases
Case

- A 47 year old man with AIDS (CD4 37, V.L. 90,000) presents to your clinic with fever of 103 daily for 4 weeks. He has had watery diarrhea for 6 weeks. Physical exam shows muscle wasting and splenomegaly. A CXR is normal.

  - What is the differential diagnosis?
  - What should you do now?
HIV/AIDS Fever Differential Diagnosis

- M. avium Bacteremia
- Miliary Tuberculosis
- Disseminated Pneumocystis
- Cryptococcosis
- Disseminated Coccidioidomycosis
- Bacillary Angiomatosis
- CMV
- Non-Hodgkin’s Lymphoma
Fever Physical Exam

- Adenopathy may suggest MAC or TB
- Retinal lesions may suggest CMV
- Umbilicated skin lesions suggest cryptococcosis
- Purple-red raised nodules suggest bacillary angiomatosis
Tuberculous adenitis
Cutaneous Cryptococcosis
Bacillary Angiomatosis
NAIHS HIV/AIDS
Initial Fever Evaluation

- CMP, CBC, CXR, Blood Cultures
- Bactec Blood Culture
- PPD skin test
- Lumbar Puncture
- Sputum induction for PCP and AFB
- Dilated fundoscopic exam
NAIHS HIV/AIDS
Fever Evaluation continued

- Abdominal CT
- Bone Marrow
- Consider:
  - Liver biopsy
  - Skin biopsy
  - Endoscopy
M. avium Review

- Slow growing Acid-Fast Bacillus seen when CD4 <50

- Patients present with fever, sweats and chronic diarrhea.

- Cachexia, hepatosplenomegaly and lymphadenopathy are often seen on physical exam.

- Pancytopenia and elevated alkaline phosphatase are
MAC Diagnostics

- Bactec Blood cultures are the test of choice.
  - Positive in 7-10 days
- Other cultures helpful but invasive:
  - Bone Marrow: Positive in 17 of 30 blood culture positive cases
  - Gut biopsy useful to document mucosal invasion
- Sputum and stool Cx are not reliable.
- CT Abdomen: Adenopathy seen in 42% of cases
MAC Therapeutics

- Basic Therapy
  - Clarithromycin 500 mg po BID
    - Plus
  - Ethambutol 15-20 mg/kg po QD
MAC Therapeutics

- **Treatment Options:**
  - Addition of Rifabutin 300 to 450 mg po QD is optional if > 100 organisms per ml or HAART ineffective.
  - Azithromycin: if GI intolerance or drug interactions
  - Treat until CD4 > 200 for 6 months and cultures negative for 12 months
MAC Therapeutics

- Salvage Regimen
  - Amikacin 10 mg/kg iv QD
    - *plus either*
  - Ciprofloxacin 500 mg po BID
    - *or*
  - Rifabutin 300-450 mg po QD
MAC Prevention

- Start Azithromycin 1200 mg po weekly if CD4 < 50

- Stop Prophylaxis if CD4 > 100 for 3 months
Case Presentation

- A 42 year-old man is referred to ID clinic with a positive PPD at 10 mm after being exposed to a case of active pulmonary TB. He has a history of reactive arthritis but is not on immunosup pressive therapy. Review of symptoms is completely negative and physical exam is unremarkable. A CXR is normal. He is offered Isoniazid therapy but declines.
Nine months later the patient presents with chronic cough and fever. On exam he is tachycardic and has diffuse rales. A CXR is obtained…
HIV Pulmonary Infiltrate Differential

- Bacterial pneumonia
- Tuberculosis
- M. kansasii
- Pneumocystis
- Toxoplasmosis
- Cryptococcosis
- Coccidioidomycosis
- Blastomycosis
- Aspergillosis

- Strongyloidiasis
- CMV
- VZV
- Kaposi’s Sarcoma
- Lymphoma
- Lymphocytic Interstitial Pneumonitis
Initial evaluation of infiltrates

- Routine Gram stain and culture
- Blood cultures
- Sputum AFB smear and culture X 3
- Induced sputum for PCP immunofluorescence
HIV Pulmonary Infiltrate Therapy

- Typical pneumonia, high CD4 count
  - Third generation cephalosporin plus a macrolide

- Atypical pneumonia, low CD4 count
  - Trimethoprim/Sulfa plus a cephalosporin plus a macrolide
HIV: Further Infiltrate evaluation

- What to do next if routine tests are negative
  - Bronchoalveolar Lavage
  - Transbronchial lung biopsy
  - Transcutaneous lung biopsy
Case Presentation

- The patient is admitted and treated empirically for bacterial pneumonia with Ceftriaxone/Azithromycin and for *Pneumocystis jiroveci* with Trimethoprim/Sulfa. Sputa are induced for AFB and the smears are positive. The CD4 count comes back at 197. The patient is started on INH, Rifampin, pyrazinamide and ethambutol. Tenofovir, Emtricitabine and Efavirenz are started 2 weeks later. Cultures grow *Mycobacterium tuberculosis*
Case Presentation

- The patient has a rapid improvement in his fevers and cough. One month later in clinic he notes worsening cough and exam reveals low grade fever and bronchial breath sounds. A F/U CXR shows a new cavity in the right mid lung zone.
HIV and Tuberculosis Epidemiology

- 2010 worldwide
  - 34 million people living with HIV
  - 8.8 new cases of tuberculosis
  - 1.1 million of the new cases also had HIV
  - 350,000 HIV patients died of TB

- HIV increases the RR of TB infection by 20 to 30-fold
TB/HIV Clinical Presentation

- TB in early HIV behaves like HIV (-) disease
  - Cough
  - Hemoptysis
  - Fever
  - Night sweats
  - Weight loss
  - Upper lobe pulmonary disease with cavitation
TB/HIV Clinical Presentation

- TB in late HIV disease is different
  - Looks like primary TB
    - Lymphadenopathy present on exam and CXR
    - Miliary pattern
    - Cavitation is less frequent

- Extrapulmonary sites involved in 40-80%:
  - Lymph nodes, brain, meninges, pericardium, abdomen
TB/HIV Clinical Presentation

- Subclinical TB disease is common in HIV
- Smear negative disease is more common in HIV
- 22% of patients with HIV and TB have a normal CXR
Diagnosis of TB

- Sputum AFB x 3 in 24 hours including one early AM
  - 2 sputa may be adequate—“Front loading” (Miremba et al)
- Culture
  - BACTEC and MGIT technology
- Nucleic Acid Amplification
  - CDC recommends sending one on every patient
  - Xpert MTB/RIF assay approved by FDA in July 2013
Treatment of TB in HIV

- Latent TB
  - Diagnosis with PPD or IGRA (quantiFERON assay)
  - Rule out active TB first
  - Treat with INH for 9 months
Drug interactions

- Rifampin lowers the drug levels of cyp3a4 metabolized drugs including efavirenz, protease and integrase inhibitors, dilantin, opiates, steroids and other drugs.

- Rifabutin metabolism is inhibited by ritonavir
  - Dose cut 50% and give daily, not thrice weekly
Treatment of TB in HIV

- If already on Efavirenz
  - Use INH, PZA, EMB and RIFAMPIN 600 mg po daily

- If already on a boosted Protease Inhibitor
  - Use INH, PZA, EMB and RIFABUTIN 150 mg po daily

- If on an integrase inhibitor
  - Do not treat with boosted elvitegravir
  - Limited experience with Raltegravir and Dolutegravir and rifamycins
Drug interactions for HIV treatment naive

- Efavirenz is no longer a first line HIV drug
- Raltegravir, Dolutegravir and Elvitegravir/cobicistat all interact with Rifampin
- Consider using:
  - Tenfovir/Emtricitabine plus Boosted Darunavir for the HIV and Rifabutin 150 mg po daily for the TB
  - Tenofovir/Emtracitabine/Efavirenz for the HIV and Rifampin 600 mg po daily for the TB
If you need further assistance...
Don’t call me, Call Marcos Burgos!!
Immune Reconstitution Inflammatory Syndrome

- Re-awakening immune syndrome unmasks or causes paradoxical disease:
  - Cryptococcal meningitis
  - PML (JC virus)
  - PCP
  - CMV retinitis/gastroenteritis
  - Tb and MAC

- Risk Factors: low CD4, high viral load, HLA -B44
Immune Reconstitution Inflammatory Syndrome

Two TB syndromes:

- Subclinical TB is unmasked after anti HIV therapy is started
  - Fever, adenopathy, pulmonary, neurologic symptoms

- Paradoxical worsening of pre-existing TB after starting ARVs
  - New cavitation
  - Hypercalcemia is a hallmark.
  - Can occur even in HIV negative patients with anti Tb therapy
Immune Reconstitution Inflammatory Syndrome

- **Prevention**
  - Start TB therapy right away
  - Delay start of HIV Therapy
    - CD4 count < 50 → Start antiretrovirals by ≤ 2 weeks
    - CD4 count ≥ 50 → Start antiretrovirals by 8-12 weeks

- **Treatment**
  - NSAIDS
  - Steroids
Case presentation

- A 53 year old woman with HIV now has diarrhea. She was treated with ZDV/3TC/NFV originally but now is on a second regimen including TDF/FTC/ATZ/rtv. She notes 6 weeks of watery stools without fever or blood.
  - What is the differential diagnosis?
  - What should you do now?
HIV/AIDS Diarrhea

- **Chronic**
  - CMV
  - Microsporidium
  - Cryptosporidium
  - MAC
  - Isospora
  - Cyclospora
  - Giardia

- **Acute**
  - Shigella
  - Salmonella
  - Campylobacter
  - C. Difficile
HIV/AIDS Diarrhea

- **Bloody**
  - Shigella
  - Salmonella
  - Campylobacter
  - C. difficile
  - CMV
  - Entamoeba

- **Watery**
  - Microsporidia
  - Cryptosporidium
  - MAC
  - Isospora
  - Giardia
  - Entamoeba
  - Cyclospora
HIV/AIDS Diarrhea work up

- Initial evaluation
  - CBC, electrolytes, BUN, Creatinine, LFTS
  - Routine stool culture
  - Clostridium difficile toxin assay
  - Stool Ova and Parasites exam
  - Stool Trichrome stain
  - Stool Modified AFB Stain
HIV/AIDS  Diarrhea workup

- Further workup
  - Upper endoscopy with small bowel Bx.
  - Colonoscopy with Bx.
Microsporidiosis

- Spore forming protozoan with fungal characteristics
- Ubiquitous in the environment
- 1-2 microns in size
- Two species
  - *Enterocytozoan bieuneusi* - major cause of diarrhea
  - *Encephalitozoan cuniculi and hellem* - disseminate
- Distort small bowel villous architecture
Microsporidiosis
Microsporidiosis

- Clinical syndrome:
  - Profuse watery diarrhea
  - Median CD4 is 20
  - Biliary, lung, corneal, renal disease and encephalitis all occur

- Diagnosis
  - Modified trichrome stain
Microsporidiosis

- Treatment
  - Albendazole 400 mg po bid for Encephalocytozoan sp
  - No reliable Rx for Enterocytozoan bienusi
Cytomegalovirus colitis

- CMV is a herpesvirus that infects latently
- AIDS patients affected when CD4 <50
- CMV viremia is a risk factor for subsequent invasion
Cytomegalovirus

- Clinical Manifestations
  - Esophagitis with odynophagia, fever and nausea
  - Gastritis with epigastric pain but rarely bleeds
  - Enteritis of small bowel: pain and diarrhea
  - Colitis: fever, weight loss, watery diarrhea and hemorrhage
Cytomegalovirus colitis

- **Diagnosis:**
  - PCR of blood
  - Biopsy: cytomegalic cells with eosinophilic intranuclear and basophilic cytoplasmic inclusions.
Cytomegalovirus colitis
CMV Treatment

- Gancyclovir induction 5 mg/kg IV q 12 hrs then Valgancyclovir 900 mg po bid when better for 3-6 weeks
- Maintenance therapy with daily VGC for relapsed cases
- Support WBC with G-CSF
- Foscarnet is usually reserved for salvage therapy
Case presentation

- A 51 year old man with HIV develops sudden visual impairment in the right eye. He has had low grade fevers for a few weeks. His last CD4 count was 97 and the viral load is > 100,000.
Cotton Wool Spots
CMV retinitis
Acute Retinal Necrosis
Progressive Outer Retinal Necrosis
CMV Retinitis

- Affect 47% of patients with CD4 < 50

- If no HAART is given, median time to progression is 47-104 days.

- Median time to death was 0.65 years in the pre HAART era.
CMV Retinitis

- Symptoms:
  - Scotomata
  - Floaters
  - Photopsia “flashing lights”
CMV Retinitis

- Examination
  - Fluffy lesions near vessels with hemorrhage
    - Fulminant (hemorrhagic)
    - Indolent (non hemorrhagic)
    - Mixed
  - Retinal detachment
- Immune Reconstitution uveitis
  - Vitreous involvement is pathognomonic for IRIS
CMV Retinitis Treatment

- **First line:**
  - Valganciclovir 900 mg po bid for 14-21 days then 900 mg po daily until CD4 >100 for 3-6 months

- **If <1500 microns from fovea or near optic head**
  - IV gancyclovir
  - Gancyclovir injection (implants are no longer available)

- **Other drugs**
  - Foscarnet
  - Cidofovir
CMV Immune reconstitution uveitis

- Manifestations
  - Vitritis
  - Cystoid Macular edema
  - Epiretinal membranes

- Treatment
  - Steroids controversial
  - Valganciclovir
Case Presentation

- A 45 year old man with AIDS (CD4 85) now has a headache of three weeks duration. His friends say he is confused. Your neurologic exam reveals a left pronator drift.
  - What is the differential diagnosis?
  - What should you do now?
Differential for paralysis in AIDS

- **Brain**
  - Toxoplasmosis
  - Lymphoma
  - TB
  - Cryptococcosis
  - Nocardia
  - Brain abscess
  - PML

- **Upper motor neuron**
  - Vacuolar myelopathy
  - TB
  - Lymphoma
  - Epidural abscess

- **Lower Motor Neuron**
  - CIDP
  - Mononeuritis multiplex
  - CMV polyradiculopathy
Evaluation of paralysis in AIDS

- **Initial work-up**
  - Head CT scan
  - Lumbar Puncture

- **Further work-up**
  - MRI of brain or spine for upper motor neuron Dz
  - NCV/EMG for lower motor neuron Dz
Brain Mass Lesion

- Three major clinical entities
  - Toxoplasmosis:
    - More often multiple
  - Primary CNS Lymphoma (PCNSL)
    - Half the time solitary
    - If $\geq 4\text{cm}$, PCNSL is more likely
  - Progressive Multifocal Leukoencephalopathy
    - Usually non-enhancing
    - Will enhance if IRIS is present after institution of ART
Brain Mass Lesion Evaluation

- If no mass effect, proceed with LP and treat
  - Toxo PCR (+) → toxoplasmosis
  - EBV PCR (+) → CNS lymphoma
  - JC PCR virus (+) → PML

- If mass effect and herniating, proceed with brain biopsy

- If mass effect and not herniating and Toxo serum Ab positive → a trial of anti toxo Rx
Toxoplasmosis

- Caused by *Toxoplasma gondii* a protozoan
- Causes latent infection, reactivates when CD4 < 100
- Acquired through exposure to cats and eating poorly cooked meats
Toxoplasmosis
Clinical manifestations

- **Encephalitis:**
  - headache, confusion, fever, dull affect

- **Pneumonia**
  - Fever and dry cough
  - Reticulonodular infiltrate

- **Chorioretinitis**
  - Yellow, cotton-like infiltrates
Toxoplasmosis

**Diagnosis**
- Serology
- CT or MRI with contrast
- SPECT or PET: (decreased thallium uptake and glucose use with toxo)
- Biopsy: 3-4% morbidity rate
- PCR: 50-98% sensitive, 96-100% specific
Toxoplasmosis

- **Treatment**
  - Pyramethamine 200 mg po x1 then 50-75 mg po daily
  - Sulfadiazine 1-1.5 gm po qid
  - Leukovorin 10-25 mg po daily

- Clindamycin is substituted for sulfadiazine if sulfa allergic
Three more paralysis syndromes

- Vacuolar myelopathy: Upper motor neuron
  - spastic
  - hyper-reflexic
  - no pleocytosis
  - normal glucose
Vacuolar Myelopathy
Three more paralysis syndromes

- Chronic Inflammatory Demyelinating Polyneuropathy
  - Looks like Guillain Barre Syndrome
    - Flaccid
    - Areflexic
    - High CSF protein is the hallmark
  - Pretty good prognosis with treatment
Three more paralysis syndromes, contd

- **CMV Polyradiculopathy**
  - Flaccid
  - Areflexic
  - Polys in CSF suggesting bacterial meningitis
  - Low glucose suggesting bacterial meningitis

- **CMV Ventriculoencephalitis**
  - Polys in CSF and low glucose
  - Periventricular enhancement
CMV Encephalitis
Three more paralysis syndromes

- **Treatment**
  - Vacuolar Myelopathy: ART
  - CIDP: ART plus steroids and plasmapheresis
  - CMV Polyradiculopathy: ganciclovir +/- foscarinet