HIV-Associated Opportunistic Infections: Part II

Rajesh T. Gandhi, MD
Massachusetts General Hospital
Professor of Medicine, Harvard Medical School
Boston, Massachusetts

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Disclosures of Financial Relationships with Relevant Commercial Interests

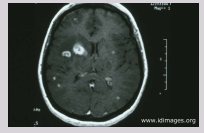
- None

HIV Associated Opportunistic Infections: Part 2

- **Opportunistic CNS Infections: Brain Lesions**
- **Cryptococcal Infections**
- **Mycobacterial Infections**
- **Immune Reconstitution Inflammatory Syndrome**
- **Cytomegalovirus (CMV)**

Question #1

- 50-year-old M with HIV (CD4 40, HIV RNA 60,000 not on antiretroviral therapy) now with fever, headache
- Northeast US, no travel; no animal, TB exposures
- MRI: ring enhancing lesions; no midline shift
- Serum toxoplasma (toxo) IgG +



What would you recommend?

A. Brain biopsy
B. Meningeal biopsy
C. Initiate anti-toxo therapy; if no response in 2 weeks, brain biopsy
D. Vancomycin, cefepime, metronidazole
E. Liposomal amphotericin and 5FC

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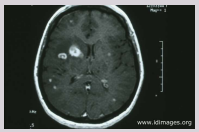

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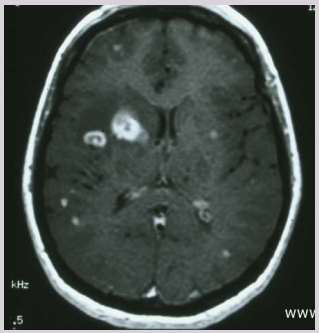
Brain Lesions in People with HIV (PWH)

- MRI with contrast favored over CT (CT without contrast: miss lesions)
- Clues:
  - **Toxoplasma:** multiple ring enhancing lesions, often involving basal ganglia; serum toxoplasma IgG positive (reactivation)
  - **Primary CNS lymphoma:** large solitary focal brain lesion; may cross corpus callosum; increased FDG PET uptake; B cell lymphoma; CSF EBV PCR+. CD4 cell count <50
  - **Tuberculoma:** consider in person from endemic area with contrast enhancing lesions, basilar meningitis
  - **Progressive multifocal leukoencephalopathy (PML):** asymmetric non-enhancing lesions in subcortical white matter without mass effect

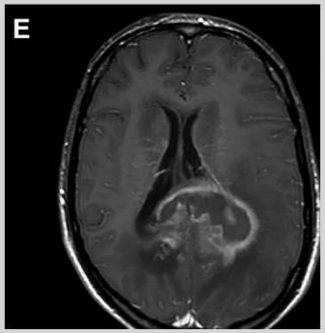
Siripurapu R and Ota Y, Neuroimag Clin N Am, 2023

Toxoplasma Encephalitis



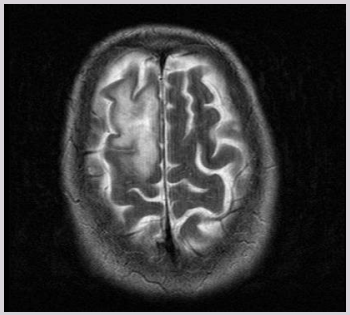
www.idimages.org

Primary CNS Lymphoma

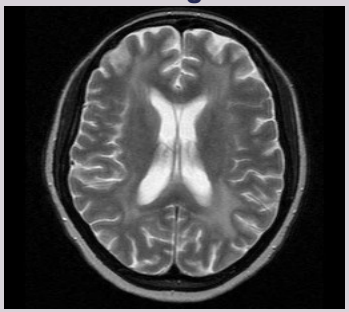


Siripurapu R and Ota Y, Neuroimag Clin N Am, 2023

PML: Asymmetric White Matter Changes Adjacent to Cortical Ribbon No Mass



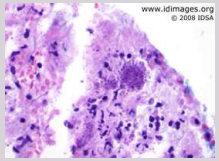
HIV Encephalitis: Bilateral Symmetric White Matter Changes



www.idimages.org. Contributed by Dr. Vince Marconi

Toxoplasma Encephalitis (TE)

- Caused by **protozoan, *Toxoplasma gondii***
- Reactivation of latent tissue cysts
- Highest risk is in PWH with **CD4 count <100**
- Headache, confusion, weakness, fever
- Diagnosis:
  - **Serum toxoplasma IgG usually positive**
  - **CSF toxoplasma PCR:** high specificity (96-100%); sensitivity 50-60% (negative PCR does not rule out TE)
  - **Empiric diagnosis:** clinical, radiographic improvement with anti-toxoplasma therapy; if no response by about 2 weeks, consider brain biopsy



https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/toxoplasma-gondii?view=full

Toxoplasma Encephalitis: Therapy

- **Preferred Regimen**
  - Sulfadiazine plus pyrimethamine plus leucovorin (PO only)
    - May be unavailable or excessively expensive
  - Trimethoprim-sulfamethoxazole (PO or IV)
  - In patients with sulfa allergy, sulfa desensitization should be attempted

Note: Initiate antiretroviral therapy when patient is tolerating anti-toxoplasma therapy (usually within a week or two after starting anti-toxoplasma therapy)

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/toxoplasma-gondii?view=full

Primary Prevention of Toxoplasmosis in PWH

- **Indication**
  - Positive Toxoplasma IgG and CD4 <100 cells/uL
- **Drugs**
  - First Choice: **TMP-SMX** (one double strength tablet daily)
  - Alternatives
    - Other dosing regimens for TMP/SMX
    - Dapsone-Pyrimethamine (with leucovorin)
    - Atovaquone +/- Pyrimethamine (with leucovorin)

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/toxoplasma-gondii?view=full

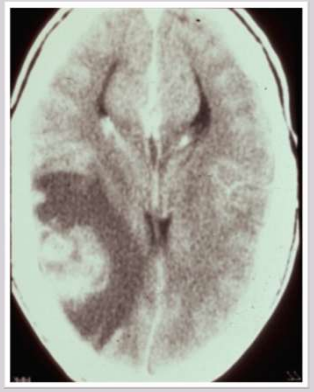
Primary Prevention of Toxoplasmosis in PWH

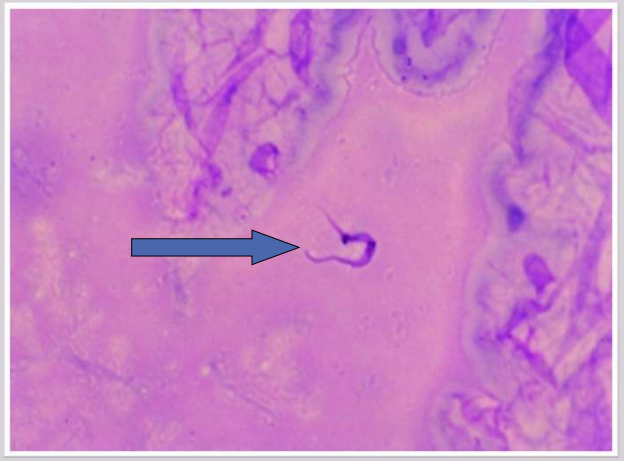
- For patients with CD4<200 who are on TMP-SMX or atovaquone for PCP prophylaxis
  - Nothing more is needed
- For patient on Aerosol Pentamidine or Dapsone for PCP prophylaxis
  - If on dapsone: add pyrimethamine (plus leucovorin)
  - If on Aerosol pentamidine because cannot take TMP-SMX: not protected
    - Consider switching to atovaquone if seropositive for toxo

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/toxoplasma-gondii?view=full

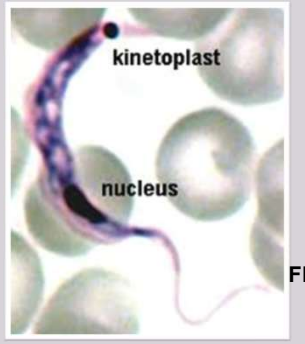
Case Study

- A 39-year-old female from Brazil presents to ED with seizure.
  - HIV Ag/Ab positive
  - CD4 count 20/μL
  - HIV RNA 100,000 copies/μL
- Started on sulfadiazine, pyrimethamine.
- After 14 days, not improved; brain biopsy performed

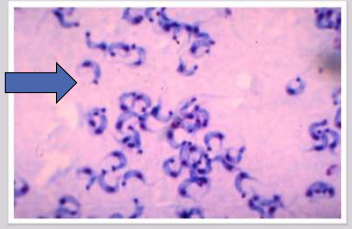




Trypanosoma cruzi in Blood Smear and CSF (Chagasic Encephalitis in PWH)



Flagellum



Badero et al, AIDS THERAPY, 4th Ed
DiazGranados C, Lancet ID, 2009

Cryptococcal Infections

Question #2

- 50-year-old woman with HIV (CD4 20, HIV RNA 500,000) presents with fever and headache. Not on antiretroviral therapy (ART). Diagnosed with cryptococcal meningitis
- Started on induction therapy (liposomal amphotericin plus 5FC)

When should she be started on ART?

A. Start ART at same time as anti-fungal therapy
B. About 4 weeks after starting anti-fungal therapy
C. 10 weeks after starting anti-fungal therapy
D. 6 months after starting anti-fungal therapy
E. After completing maintenance anti-fungal therapy

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HIV-Associated Cryptococcal Meningitis

- Usually presents with **subacute onset** of confusion, lethargy
- Neck stiffness and photophobia only occur in 25%
- **CD4 Count <100 cells/uL** in 90% of patients
- CSF: minimal abnormalities or lymphocytic pleocytosis with elevated protein.
- Opening pressure >25 cm H_20 in 60-80% of patients (be sure to measure)
- Serum and CSF cryptococcal antigen positive in almost all patients.
  - High sensitivity and specificity.
  - False positives uncommon (cross-reactive infection: Trichosporon species)
- Blood cultures positive for cryptococcus in 60%

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis?view=full

Therapy of Cryptococcal Meningitis

Liposomal Ampho B 3-4 mg/kg daily plus **Flucytosine*** 25 mg/kg QID	→	2 weeks	Induction
Fluconazole 800 mg po qd**	→	≥8 weeks	Consolidation
Fluconazole 200 mg po daily***	→	≥ 52 weeks	Maintenance

***5FC Associated with earlier sterilization CSF, fewer relapses, improved survival**

****For clinically stable patients with negative CSF cultures, dose can be reduced to 400 mg daily**

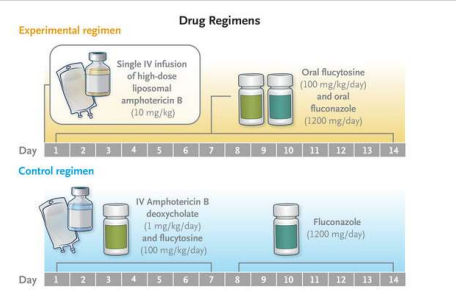
*****Stop after at least 1 yr total therapy if patient asymptomatic, CD4 >100, suppressed HIV RNA on ART**

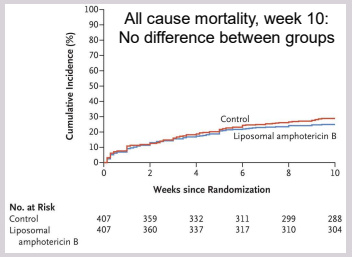
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Single-dose Liposomal AmB with Fluconazole/5FC

Preferred in Resource-limited Health Care Systems (WHO)

AMBITION Trial (n=814 participants)





Adverse events less frequent in single-dose AmB group

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Jarvis JN et al, NEJM, 2022

Management of Cryptococcal Meningitis

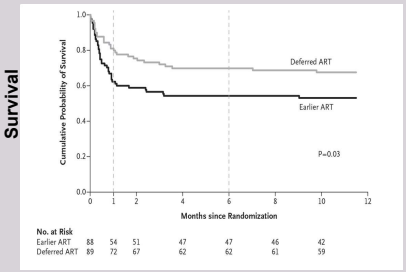
- Patients in hospital for at least 7 days and ideally 14 days
- Lumbar puncture at day 7 and 14
- In patients with symptoms of elevated intracranial pressure and opening pressure >25 cm: remove CSF to reduce pressure by half or <20cm H20
  - Lumbar drain or VP shunt may be needed if pressures remain elevated
- Successful induction therapy = clinical improvement, negative CSF culture
- CSF CrAg frequently positive at Week 2: not indicative of failure
- Monitoring of cryptococcal antigen titers not recommended

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis?view=full

When to Start ART for Cryptococcal Meningitis

- DHHS OI Guidelines: ART initiation 4-6 weeks after initiation of antifungal therapy
- Some experts start ART at 2-4 weeks after initiation of anti-fungal therapy with ART initiation at 2 weeks for those who have clinically improved, have control of intracranial pressure, have negative CSF cultures and can be closely monitored

COAT trial: early ART (1-2 wks) associated with higher mortality than delayed ART (5 wk)



Boulware D et al, NEJM, 2014

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SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Gandhi RT et al, IAS USA Guidelines, JAMA 2024

Preventing Disease

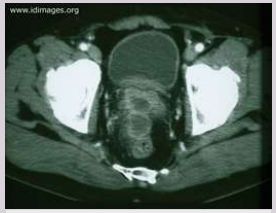
(Pre-emptive Therapy for Cryptococcal Ag+/ Low CD4 Cell Count)

- **Patients with CD4 count <200: check serum cryptococcal antigen**
  - Frequency of + Ag: 2.9% if CD4 <100
  - Positive serum CrAg predicts development of disease
- **If Positive: Perform LP and Blood Cultures to determine Rx**
  - If CSF positive or serum CrAg by LFA ≥1:640: Treat like cryptococcal meningitis/disseminated (Ampho/5FC)
  - If CSF negative: fluconazole 800 to 1200 mg daily for 2 wks, then 400 to 800 mg daily for 10 wks, then 200 mg daily (total 6 months)

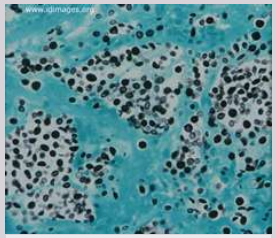
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis?view=full

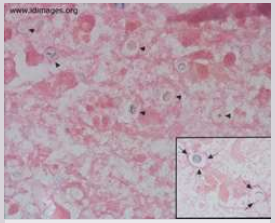
Cryptococcal Prostate Abscess

- Man with advanced HIV, CD4 cell count 40, HIV RNA 225,000 (not on ART) presented with 4 weeks of pain on defecation



Pelvic CT Scan: Prostate Abscess


Silver Stain of Prostatic Aspirate

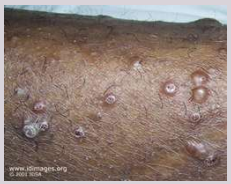

Hematoxylin and Eosin Stain

www.idimages.org

Mucocutaneous Cryptococcus

Man with advanced HIV, CD4 count <20 (not on ART) presented with fever, cough and skin lesions





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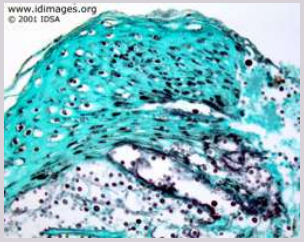
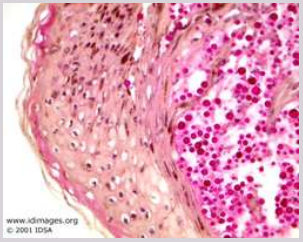


Silver Stain of Skin Biopsy



Mucicarmine Stain of Biopsy

www.idimages.org

Mycobacterial Infections

Tuberculosis in PWH: Highlights

- TB reactivation: ≈5-10%/year; may occur when CD4 count >200
- Screen for latent TB (tuberculin skin test, TST, or IGRA); if CD4 count low, repeat TB screening after immune reconstitution on ART
- TB prophylaxis: +TST (>5 mm) or IGRA; close contact of person with active TB
- When to start ART
  - CD4 count <50: start within 2 weeks of TB therapy
  - CD4 count >50: start within 2-8 weeks of TB therapy (most start sooner)
- TB Meningitis: high mortality; start ART once meningitis under control, at least 2 weeks after initiating TB treatment; close monitoring needed
- Prednisone may prevent TB immune reconstitution inflammatory syndrome

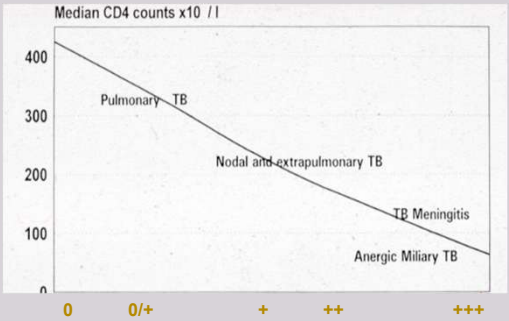
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/mycobacterium?view=full
Torok et al, CID, 2011; Meintjes NEJM, 2018

Antiretroviral /TB Drug Interactions: Selected

TB Drug	Antiretrovirals
Isoniazid	•No interactions
Rifampin	•Nucleoside RT inhibitors (TAF with caution) •Dolutegravir, Raltegravir: twice daily •Protease inhibitors: not recommended
Rifabutin	•Nucleoside RT inhibitors (TAF with caution) •Dolutegravir, Raltegravir – no change in dose •PIs with RTV – dose adjust rifabutin •PIs with cobicistat – do not coadminister
Pyrazinamide, Ethambutol, Moxifloxacin	•No interactions

Adapted by Dr Barbara Taylor from: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection.

Extrapulmonary TB and High Organism Load More Common in PWH with Low CD4 Count



Jones et al, Am Rev Respir Dis, 1993; Perlman et al, CID, 1997

Question #3

- 45-yo man with HIV (CD4 11, HIV RNA 300,000); fever, diarrhea and weight loss.
- No known TB exposure
- Started on dolutegravir + tenofovir/emtricitabine
- 2 wk later: enlarged supraclavicular lymph node
- Biopsy: necrotizing granulomas and AFB

What would you recommend?

A. Stop ART; initiate treatment for MAC
B. Stop ART; initiate MAC treatment, steroids
C. Continue ART; initiate treatment for MAC
D. Continue ART; start MAC treatment plus steroids
E. Start steroids; stop all other treatments

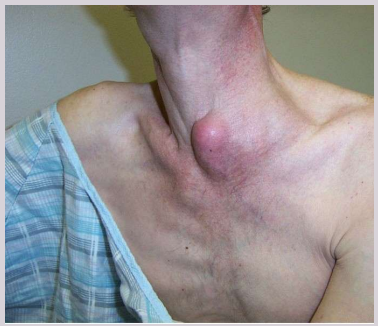


Image from Riddell J, J Translational Med, 2007

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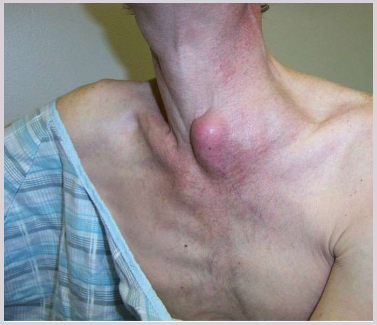


Image from Riddell J, J Translational Med, 2007

Mycobacterium Avium Complex

- **Epidemiology**
  - Ubiquitous in environment
- **Transmission**
  - Inhalation, ingestion
- **Risk factors**
  - CD4 cells <50, HIV RNA >1000
- **Clinical Manifestations of Disseminated MAC**
  - Fever, sweats, wasting, diarrhea, lymphadenopathy, hepatosplenomegaly
  - Rare cause of lung disease
  - Labs: elevated alkaline phosphatase, anemia

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/disseminated?view=full

Diagnosis

- Compatible symptoms and signs along with isolation of MAC from cultures of blood, lymph node or other normally sterile sites
- MAC may be detected in respiratory or GI tract but routine screening of these sites and pre-emptive therapy for MAC **not recommended**

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/disseminated?view=full

Treatment for MAC

- **Specific Therapy**
  - **Clarithromycin or Azithromycin + Ethambutol**
    - Rifabutin, fluoroquinolone or amikacin as a 3rd or 4th drug, particularly if severe disease (“high burden of organisms”)
    - Beware drug interactions with clarithromycin or rifabutin (azithromycin has fewer drug interactions)
    - Perform susceptibility testing on MAC isolate
- **Antiretroviral Therapy**
  - Start as soon as possible after diagnosis, preferably at the same time or within a few days of initiation of anti-mycobacterial therapy

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/disseminated?view=full

~~Primary MAC Prophylaxis~~

- Primary prophylaxis against disseminated MAC disease is NOT recommended if ART initiated immediately
- People with HIV who have CD4 cell count <50, are not on ART, who remain viremic on ART or have no options for suppressive ART should receive prophylaxis after excluding disseminated MAC
  - Preferred agents: azithromycin (few drug interactions), clarithromycin

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/disseminated?view=full

Immune Reconstitution Inflammatory Syndrome (IRIS)

Immune Reconstitution Inflammatory Syndrome (IRIS)

- Worsening manifestations or abrupt/atypical presentation of infection or tumor when ART started
  - **Paradoxical:** exacerbation of pre-existing infection or tumor
  - **Unmasking:** exacerbation of previously occult infection/tumor

Immune Reconstitution Inflammatory Syndrome (IRIS)

- **Predictors**
  - Pre therapy low CD4 cell count or high HIV RNA
  - Prior OI or recent initiation of therapy for OI
  - High pathogen load
- **Clinical Features**
  - Fevers and worsening of underlying OI or tumor
  - Usually 4-8 weeks after ART initiation; may be earlier (few days) or later

Mycobacterial IRIS

Pathogen	Typical/Characteristics of the Disease
Mycobacterium tuberculosis	• Worsening lung infiltrates, lymphadenitis, CNS tuberculomas
MAC	• Lymphadenitis; pulmonary and abdominal disease. • Bacteremia generally absent. • Elevated alkaline phosphatase may be predictive. • Severe forms of MAC IRIS with hemophagocytic lymphohistiocytosis phenotype may occur

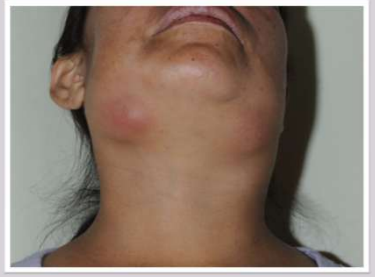
Cecil Medicine Textbook (French and Meintjes)
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/disseminated?view=full

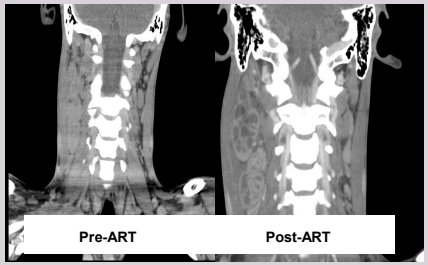
Examples of IRIS

Pathogen	Typical/Characteristics of the Disease
Cryptococcus neoformans	Worsening meningitis (may have brisk CSF pleocytosis)
Pneumocystis jiroveci	Exacerbation of pneumonia
Cytomegalovirus (CMV)	Vitritis
JC polyomavirus/PML	Worsening white matter changes; enhancement, edema
Human herpesvirus 8/Kaposi Sarcoma	Rapid progression of existing and/or new KS lesions
Varicella-zoster virus	Dermatomal or multidermatomal zoster; rarely myelitis

Cecil Medicine Textbook (French and Meintjes)
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/disseminated?view=full

MAC IRIS in a Person with HIV





Sereti I, IAS USA Topics in Antiviral Medicine, 2019

Management of IRIS

- **Evaluate for concurrent, additional OIs and tumors**
- **Treat IRIS**
  - Continue ART
  - Continue treatment of identified pathogen
  - NSAIDS or Corticosteroids

Cytomegalovirus (CMV)

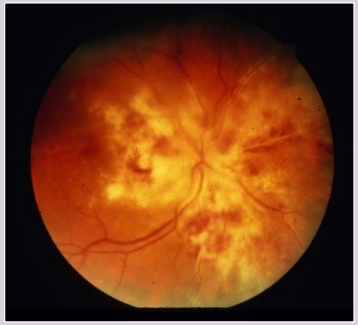
CMV in PWH: Highlights

- PWH who have CD4 count <50 and are not receiving ART
- End-organ disease:
  - Retinitis
  - GI: Colitis, Esophagitis
  - Neurologic disease
  - Pneumonitis: rare; when CMV found in bronchoalveolar lavage, frequently bystander
- Prevention: ART; valganciclovir prophylaxis NOT recommended

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cytomegalovirus?view=full

CMV Retinitis

- **Visual changes, decreased visual acuity**
- **Fundoscopic exam**
  - Bilateral disease in 1/3
  - Mustard and Ketchup
  - Necrosis of retina
  - Little vitreal inflammation
- **PCR of blood not useful: 70% sensitive, but non-specific**
- **Vitreal taps for diagnosis with PCR rarely necessary**
  - Tap positive in 80% of cases



https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cytomegalovirus?view=full

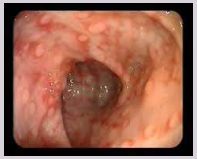
Therapy for CMV Retinitis

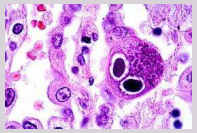
- **Immediate sight-threatening lesions**
  - ART
  - IV Ganciclovir or Valganciclovir 900 mg PO (twice daily x 14–21 days), then daily for at least 3-6 months plus
  - Intravitreal ganciclovir weekly over several weeks until lesion inactivity
  - Ganciclovir implant no longer manufactured
- **Small peripheral lesions**
  - ART
  - Oral valganciclovir for at least 3-6 months and immune reconstitution
  - +/- intravitreal ganciclovir

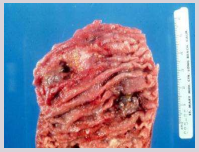
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cytomegalovirus?view=full

CMV Colitis

- **Clinical Presentation**
  - Fever, anorexia, abdominal pain, diarrhea
  - May cause perforation, hemorrhage
  - CT may show colonic thickening or mass
- **Diagnosis**
  - Colonoscopy with cytology or biopsy: mucosal ulcerations, intranuclear/intracytoplasmic inclusions, immunohistochemistry
  - PCR non-specific
- **Therapy:** Ganciclovir, Valganciclovir. Alternative: Foscarnet







https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cytomegalovirus?view=full

CMV Neurologic Disease

- **Encephalitis**
- **Ventriculoencephalitis**
  - Focal neurologic signs, rapid progression
  - Peri-ventricular enhancement on MRI or CT imaging
- **Polyradiculomyelopathy or transverse myelitis**
  - Radicular back pain, urinary retention, bilateral leg weakness
  - Spastic myelopathy, sacral paresthesia
  - CSF: neutrophilic pleocytosis (100-200), low glucose, elevated protein

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cytomegalovirus?view=full

Summary

Multiple causes of brain lesions in people with advanced HIV; empiric therapy response = dx of toxoplasma encephalitis

New approaches to treating and preventing cryptococcal meningitis; deferring ART for about 4 weeks appropriate

High risk of TB reactivation; MAC Prophylaxis no longer recommended when ART started quickly

Immune Reconstitution Inflammatory Syndrome: paradoxical worsening or unmasking of subclinical disease

CMV end-organ disease when CD4 count <50: retinitis, GI infection (colitis), neurologic disease

For More Content:

HIV Associated Opportunistic Infections: Part 3 (Online)

Mucocutaneous Infections: Candida, VZV, HSV, EBV

Endemic Mycoses

Gastrointestinal (GI) Complications