41 – HIV-Associated Opportunistic Infections

Speaker: Rajesh Gandhi, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

HIV-Associated Opportunistic Infections II

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7/1/2024

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**
- **Acknowledgement: Dr. Henry Masur for slides**

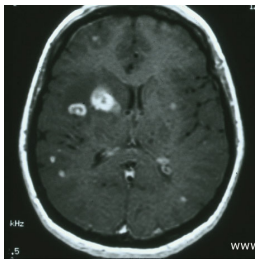
HIV Associated Opportunistic Infections: Part 2

- Opportunistic CNS Infections: Brain Lesions
- Opportunistic CNS Infections: Cryptococcal Meningitis
- Mycobacterial Infections
- Immune Reconstitution Inflammatory Syndrome

Question #1

PREVIEW QUESTION

- 50 yo M with HIV (CD4 40, HIV RNA 600,000 not on antiretroviral therapy) presents with fever, headache.
- Northeast US, no travel; no animal or TB exposures
- MRI: ring enhancing lesions; no midline shift
- Serum toxoplasma IgG +. CSF: no WBC, normal protein, toxoplasma (toxo) PCR pending
- 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

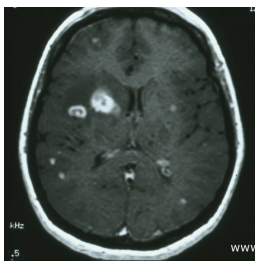


Brain Lesions in People with HIV (PWH)

- MRI with contrast favored over CT (CT without contrast may 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

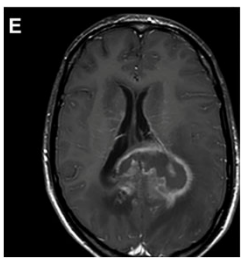
Siripurapu R and Ota Y, Neuroimag Clin N Am, 2023

Toxoplasma Encephalitis



www.idimages.org

Primary CNS Lymphoma



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

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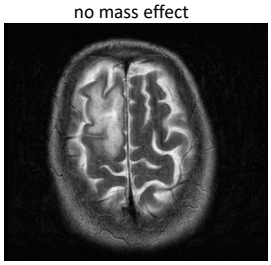
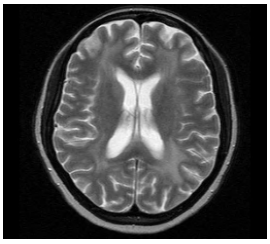
PML: Asymmetric white matter changes adjacent to cortical ribbon, no mass effect



HIV Encephalitis: bilateral symmetric white matter changes



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

Evaluation of CNS Mass Lesions in People with HIV/AIDS

- Toxoplasmosis
- Lymphoma
- Tuberculosis
- Fungus
- Nocardia
- Bacterial
- Syphilis
- Kaposi
- Chagoma
- Glioblastoma

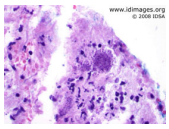
Radiologic Results
- Non-specific although certain features suggestive
- Look for Extra CNS lesions for biopsy

Laboratory Studies to Perform
- Serology: Toxo IgG
- Serum Cryptococcal Ag and Histoplasma Ag
- Blood culture - AFB
- CSF - Cryptococcal Ag
  - PCR (EBV, CMV, Toxoplasma, JC virus)

Response to Empiric Therapy

Toxoplasma Encephalitis (TE)

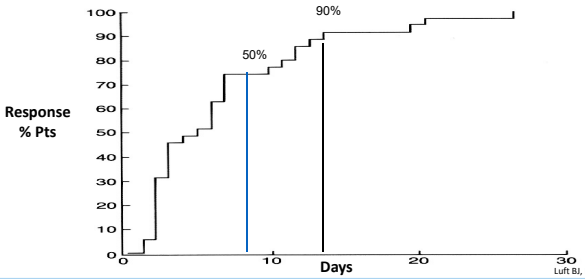
- Caused by protozoan, *Toxoplasma gondii*
- Reactivation of latent tissue cysts
- Highest risk is in PWH with CD4 count <100
- May present with headache, confusion, weakness, fever
- Diagnosis:
  - Serum toxoplasma IgG usually positive; negative serology makes TE unlikely
  - MRI: ring-enhancing lesions, often involving basal ganglia
  - 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

Time to Neurologic Response for Toxoplasma Encephalitis

35 Patients with TE Treated with Clindamycin - Pyrimethamine



Luft BJ, NEJM 1993

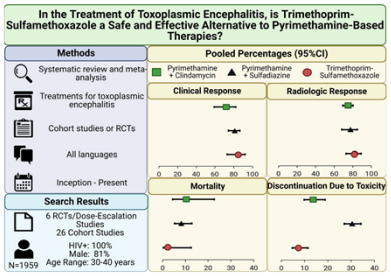
Therapy for Toxoplasma Encephalitis

- **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
- **Alternative Regimens – for those who cannot tolerate sulfonamides**
  - Clindamycin plus pyrimethamine (and leucovorin)
  - Atovaquone +/- Pyrimethamine (and leucovorin)

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

Compared with Sulfa-Pyrimethamine, Trim-sulfa has similar response rate, lower toxicity



Prosty C, CID, 2023

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Adjunctive Therapies for Toxoplasma Encephalitis

- Corticosteroids
  - Not routine
  - Only if mass effect, increased intracranial pressure/symptoms/signs
- Anticonvulsants
  - Should not be given prophylactically
  - Only if patients have seizures

Primary Prevention of Toxoplasmosis in People with HIV

- **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

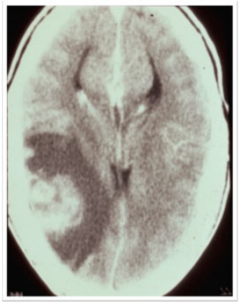
Primary Prevention of Toxoplasmosis in PWH

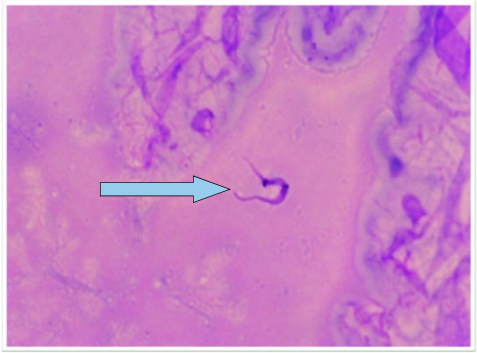
- For patients with CD4<200 who are on TMP-SMX or atovaquone for PCP prophylaxis
  - Nothing more is needed
- For patient on Aerosol Pentamidine or Dapsone for PCP prophylaxis
  - If on dapsone: add pyrimethamine (plus leucovorin)
  - If on Aerosol pentamidine because cannot take TMP-SMX: not protected-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

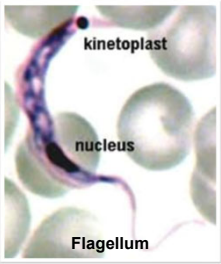
Case

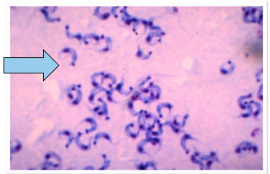
- A 39-year-old female from Brazil presents to ED with a seizure.
  - HIV Ag/Ab is positive
  - CD4 = 20/µL
  - VL = 100,000 copies/µL
- She is started on sulfadiazine and pyrimethamine.
- After 10 days, she has not improved, and a brain biopsy is performed





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





Badero et al, AIDS THERAPY, 4th Ed

DiazGranados C, Lancet ID, 2009

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HIV Associated Opportunistic Infections: Part 2

Opportunistic CNS Infections: Cryptococcal Meningitis

Question #2

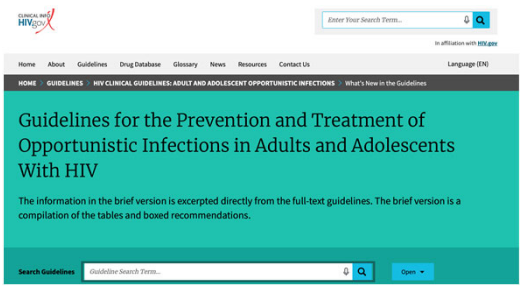
PREVIEW QUESTION

- 50-yo 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 the same time as anti-fungal therapy
  - B. About 4 weeks after starting anti-fungal therapy
  - C. 6 months after starting anti-fungal therapy
  - D. After completing a full course of maintenance anti-fungal therapy

HIV-Associated Cryptococcal Meningitis

- Usually presents with subacute onset of confusion, lethargy
- Neck stiffness and photophobia only occur in 25%
- May be accompanied by non-CNS manifestations: pneumonia, skin lesions, prostate infection
- 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.
- Blood cultures positive for cryptococcus in 60%

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



https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new

Therapy of Cryptococcal Meningitis

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

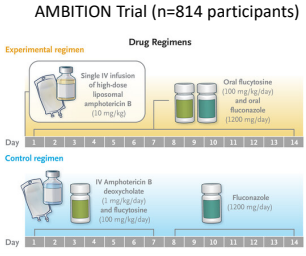
*5FC Associated with earlier sterilization CSF, fewer relapses, improved survival

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

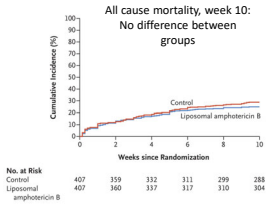
*** Stop after 12 m total therapy if CD4 >100- 150 x >3m , asymptomatic, VL <50 copies

Single-dose Liposomal AmB with Fluconazole/5FC

AMBITION Trial (n=814 participants)



Jarvis JN et al, NEJM, 2022



Adverse events less frequent in single-dose AmB group

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Management of Cryptococcal Meningitis

- For flucytosine, therapeutic drug monitoring indicated. Toxicities: marrow suppression, hepatitis, diarrhea. Renal elimination: monitor kidney function
- Successful induction therapy = clinical improvement and negative CSF culture
- India ink and CSF CrAg frequently positive at Week 2: not indicative of failure
- Monitoring of cryptococcal antigen titers not recommended
- 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
- Not routinely recommended: Corticosteroids, Mannitol, Acetazolamide

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

Dexamethasone Did Not Reduce Mortality and Was Associated with More Adverse Events and Disability

ORIGINAL ARTICLE

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

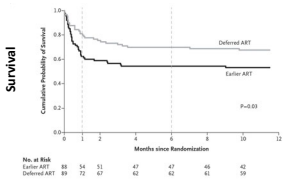
J. Beardsley, M. Wolbers, F.M. Kibengo, A.-B.M. Ggayi, A. Kamali, N.T.K. Cuc, T.Q. Binh, N.V.V. Chau, J. Farrar, L. Merson, L. Phuong, G. Thwaites, N. Van Kinh, P.T. Thuy, W. Chierakul, S. Siriboon, E. Thiansukhon, S. Onsanit, W. Supphamongkholchaikul, A.K. Chan, R. Heyderman, E. Mwinjiwa, J.J. van Oosterhout, D. Imran, H. Basri, M. Mayxay, D. Dance, P. Phimmasone, S. Rattanavong, D.G. Lalloo, and J.N. Day, for the CryptoDex Investigators*

NEJM, 2016

When to Start ART for Cryptococcal Meningitis

- DHHS OI Guidelines recommend ART initiation 4-6 weeks after initiation of antifungal therapy
- Some experts start ART earlier (at 2-4 weeks after initiation of anti-fungal therapy) based on evolving data with close monitoring

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



Boulware D et al, NEJM, 2014

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

Gandhi RT et al, IAS USA Guidelines, JAMA 2022

Preventing Disease
(Pre-emptive Therapy for Cryptococcal Ag+/Low CD4)

- **Recommendation:**
  - Screen patients with CD4 count < 100 with serum cryptococcal antigen
    - Frequency: 2.9% if CD4 <100, 4.3% if CD4 < 50
    - Positive serum CrAg predicts development of disease
- **If Positive: Perform LP and Blood Cultures to determine Rx**
  - If CSF positive or serum LFA is >=640
    - Treat like cryptococcal meningitis/disseminated (Ampho/5FC)
  - If CSF negative
    - Treat with fluconazole 400mg or 800mg x6 months

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

HIV Associated Opportunistic Infections: Part 2

Mycobacterial Infections

Tuberculosis in PWH: Highlights

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

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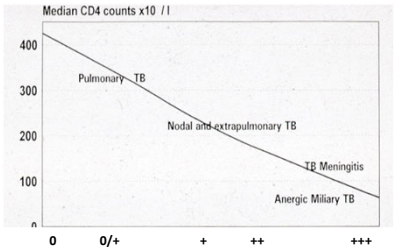
Extrapulmonary TB and High Organism Load More Common in PWH with Low CD4 Count



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) presents with fever, diarrhea and weight loss.
- He is initiated on dolutegravir + tenofovir/emtricitabine
- Two weeks later, he develops markedly enlarged supraclavicular lymph node
- Biopsy shows necrotizing granulomas and AFB; cultures grow MAC
- You recommend:
  A. Stop ART and initiate treatment for MAC
  B. Continue ART; initiate treatment for MAC
  C. Start steroids and stop all other treatments

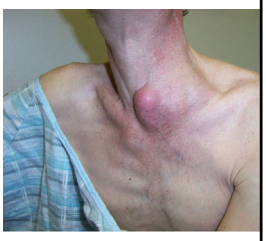


Image from Riddell J, J Translational Med, 2007

Mycobacterium Avium Intracellulare Complex

- **Epidemiology**
  - Ubiquitous in the environment
- **Transmission**
  - Inhalation, ingestion
- **Risk factors**
  - CD4 < 50, HIV RNA >1000
- **Clinical Manifestations of Disseminated MAC**
  - Fever, sweats, wasting, diarrhea, lymphadenopathy, hepatosplenomegaly
  - Rare as 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 is 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

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

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HIV Associated Opportunistic Infections: Part 2

Immune Reconstitution Inflammatory Syndrome

Immune Reconstitution Inflammatory Syndrome

- **Definition**
  - 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
- **Timing**
  - Few days to 6 months after ART initiated
  - Viral load drop more relevant than CD4 rise
    - (better lymphocyte function>number)

Immune Reconstitution Inflammatory Syndrome

- **Predictors**
  - Pre therapy low CD4 or high VL
  - Prior OI or recent initiation of therapy for OI
  - High pathogen load
- **Clinical Features**
  - Characterized by fevers and worsening of the underlying OI or tumor
  - May "unmask" disease at previously unrecognized site or lead to paradoxical worsening of a known OI
  - Usually occurs 4-8 weeks after ART initiation but may manifest earlier or later

Pathogens Commonly Associated with IRIS

- Mycobacterium avium complex
- Mycobacterium tuberculosis
- Cryptococcus neoformans
- Reported with virtually all opportunistic infections and tumors

Mycobacterial IRIS

PATHOGEN	TYPICAL/CHARACTERISTICS OF THE DISEASE
Mycobacterium tuberculosis	Worsening lung infiltrates, lymphadenitis, CNS tuberculomas
MAC	Lymphadenitis; pulmonary and abdominal disease

Cecil Textbook (French and Meintjes)

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 Textbook (French and Meintjes)

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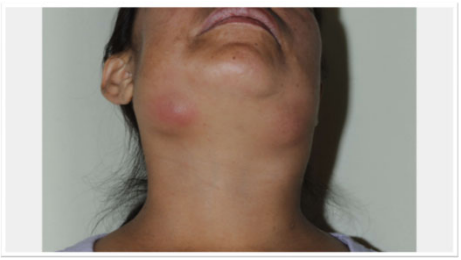
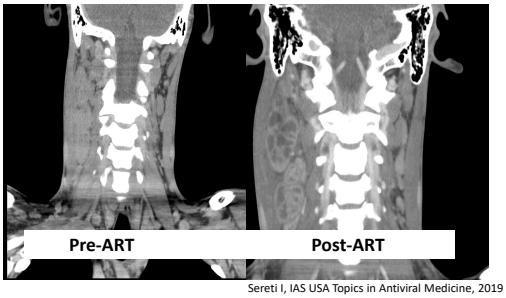
Immune Reconstitution Inflammatory Syndrome (Mycobacterium avium complex)



Sereti I, IAS USA Topics in Antiviral Medicine, 2019

MAC IRIS in Patient with HIV



Sereti I, IAS USA Topics in Antiviral Medicine, 2019

Management of IRIS

- **Reassess Diagnosis**
  - Evaluate for concurrent, additional OIs and tumors
- **Treat IRIS**
  - Continue ART
  - Continue treatment of identified pathogen
  - NSAIDS or Corticosteroids
    - Prednisone 20-40mg qd x 4-8 weeks

Summary

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

New guidelines for induction, consolidation and maintenance therapy for cryptococcal meningitis; deferring ART for about 4 weeks appropriate

TB reactivation may occur even when CD4 count >200; MAC Prophylaxis no longer recommended when ART started quickly

Immune Reconstitution Inflammatory Syndrome may occur after almost all opportunistic infections or tumors: paradoxical worsening or unmasking of subclinical disease