AETC AIDS Education & Training Center Program Southeast

HIV and Opportunistic Infections

Vidhu Kariyawasam, MD
Assistant Professor of Medicine
Division of Infectious Diseases and Global Medicine
University of Florida College of Medicine, Gainesville
Faculty, North Florida AETC

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Session Objectives

- Recognize the most common opportunistic infections (OIs)
- Discuss prophylaxis and treatment of common OIs
- Describe types of exposures and ways to prevent OIs

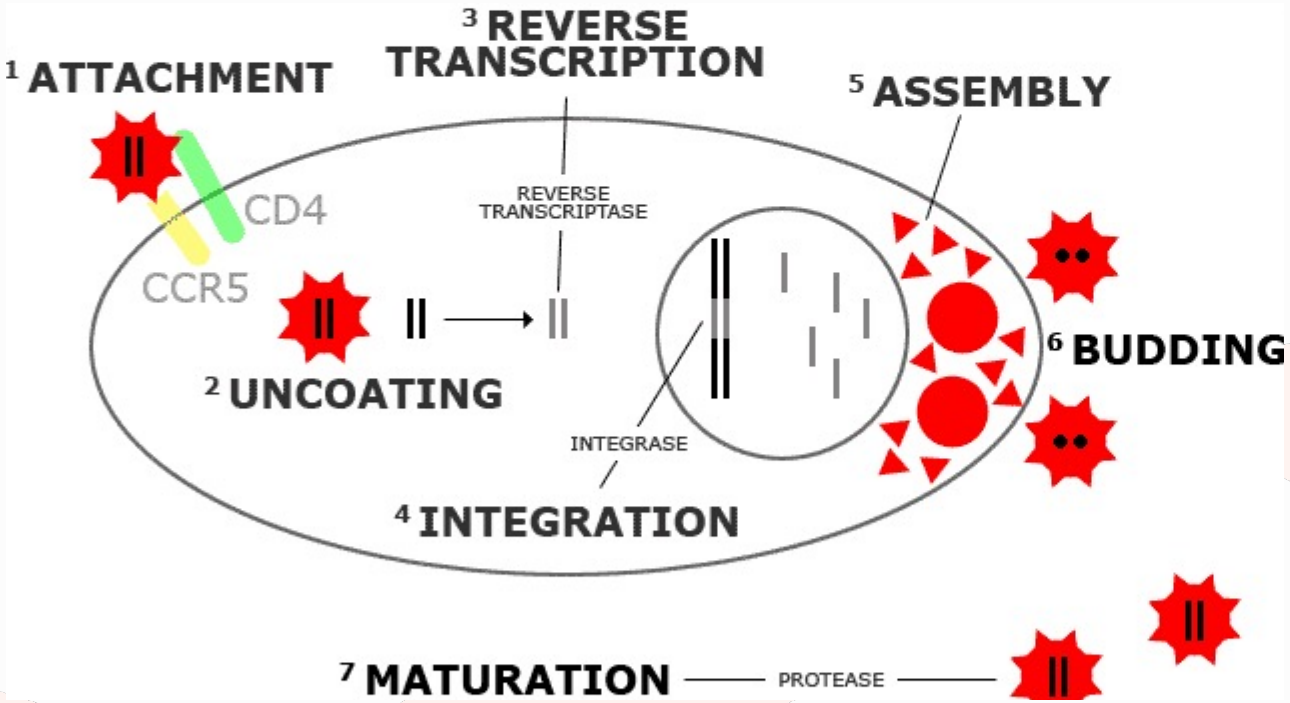
Definition: Opportunistic Infection (OI)

- Infection by a microorganism that normally does not cause disease but becomes pathogenic when the body's immune system is impaired and unable to fight off infection
- Frequently a reactivation of an infection acquired in the past which was controlled when immune system was functional (latent infection)
- Can occur de novo
- Typically caused by a low virulence organism that becomes overwhelming due to poor cell mediated immunity

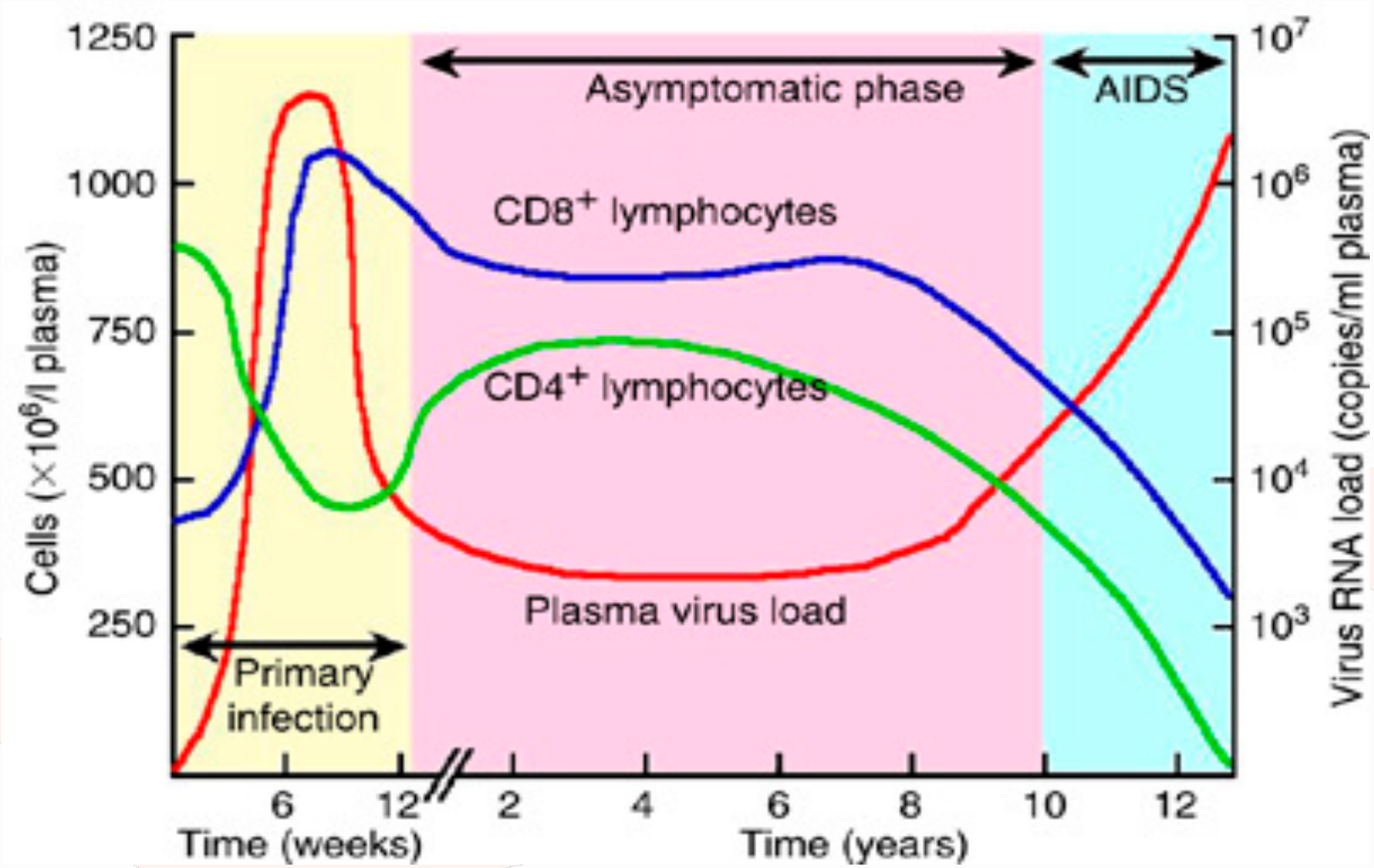
CD4 Cells

- Type of white blood cell involved in cell mediated immunity
- Normal: 500 - 1500 CD4 cells/mm^3
- Determines OI risk -Highest risk for HIV related infections occurs with CD4 < 200
- No longer used to determine need to start antiretroviral therapy (ART)

HIV Life Cycle



Typical Course of Untreated HIV- Infection



Munier ML and Kelleher AD.
Immunol Cell Biol. 2007 Jan;85(1):6-15. Epub 2006 Dec 5

2014 CDC Revised Classification System: Stage 3-Defining Opportunistic Illnesses in HIV Infection

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchia, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive+
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset age > 1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy attributed to HIV^
- Herpes simplex: chronic ulcers (present for >1 month) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site, pulmonary+, disseminated, or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* (previously known as "*Pneumocystis carinii*") pneumonia
- Pneumonia, recurrent+
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age > 1 month
- Wasting syndrome attributed to HIV

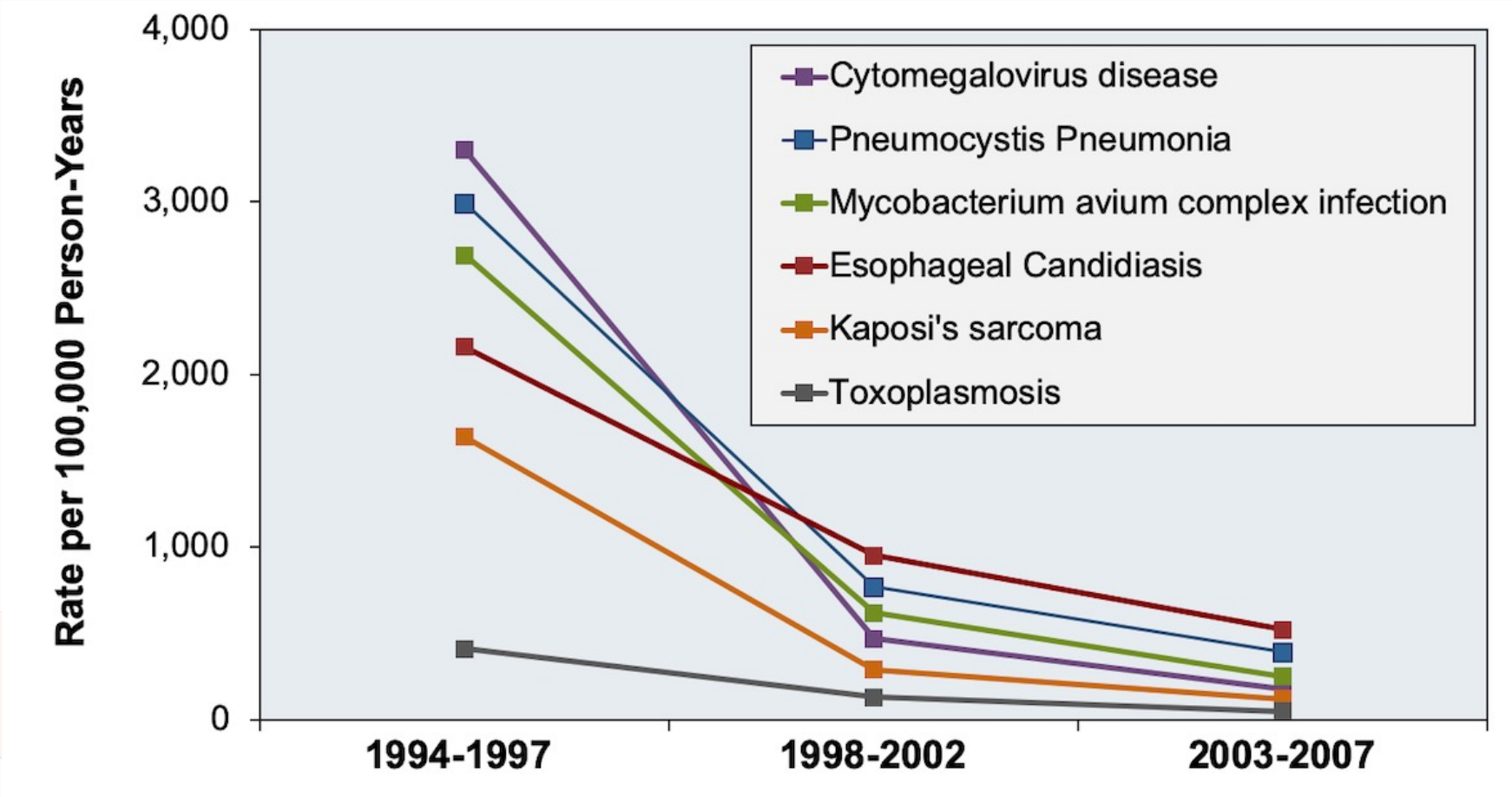
*Only among children aged < 6 years
+Only among adults, adolescents, and children aged ≥ 6 years
^Suggested diagnostic criteria for these illnesses are defined in prior surveillance case definitions

CDC.gov. Revised surveillance case definition for HIV Infection – United States, 2015. MMWR Recomm Rep. 2014;63(RR-03):1-10.

Opportunistic Infection Risk

< 500	• Tuberculosis
< 200	• *Pneumocystisis jirovecii* pneumonia (PCP)
< 100	• Toxoplasmosis • Cryptococccal meningitis
< 50	• Cytomegalovirus (CMV) Infections • *Mycobacterium avium* complex (MAC)

AIDS Defining Opportunistic Illnesses in US, HIV Outpatient Cohort Study, 1994-2007

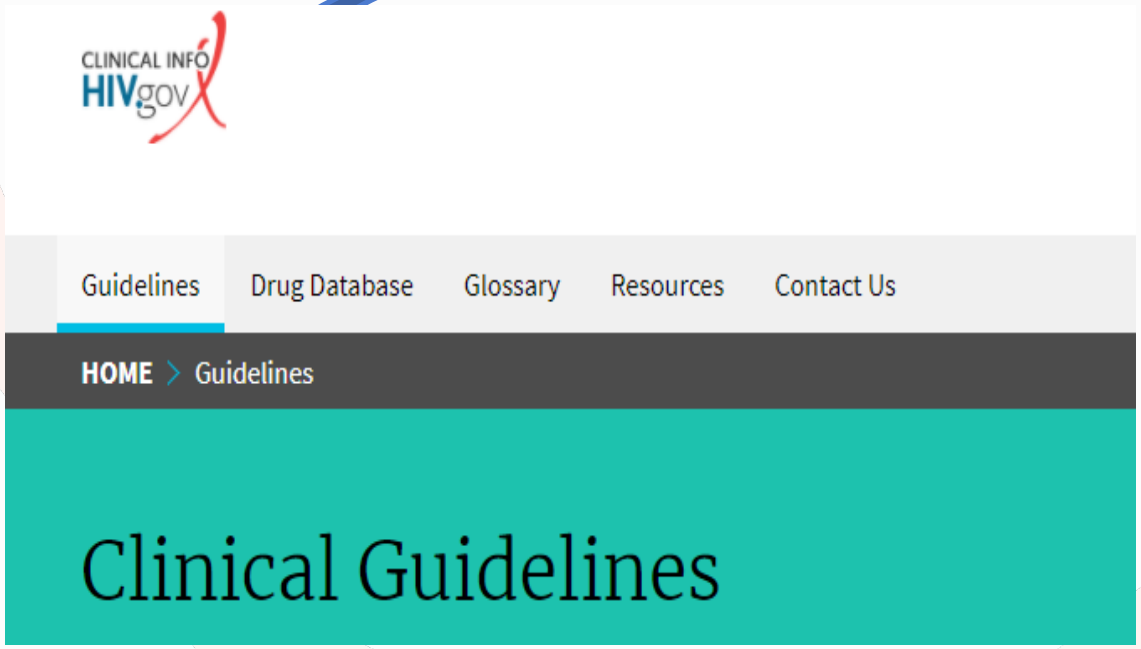


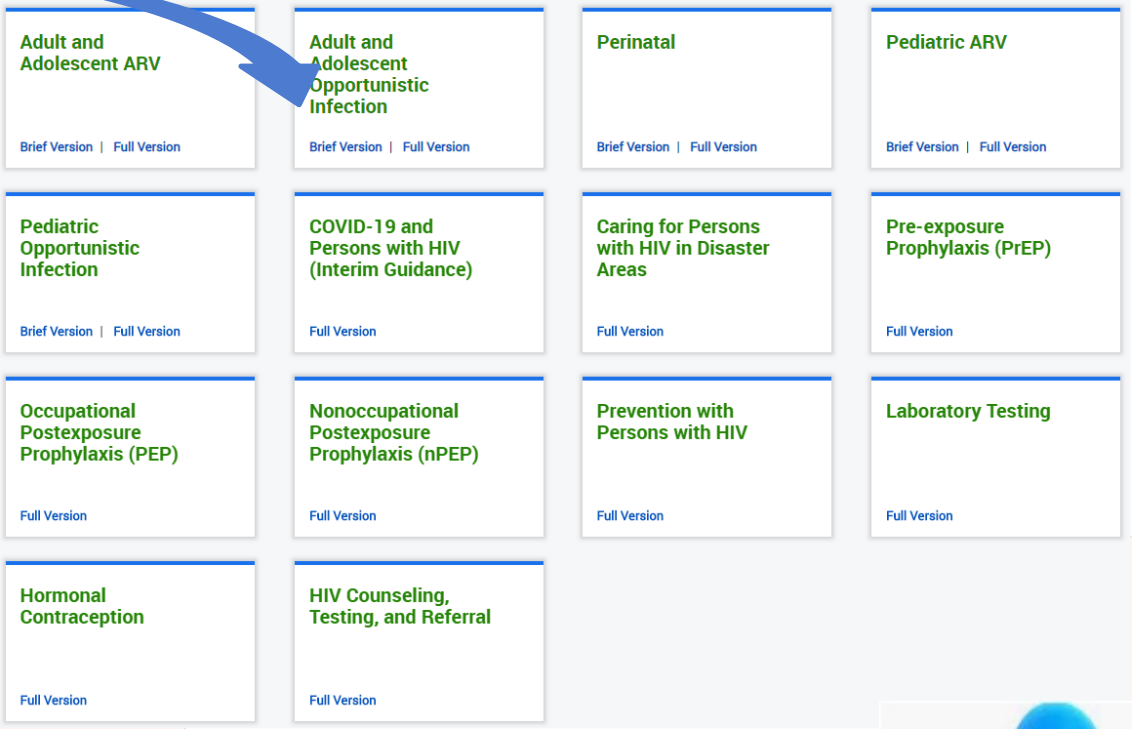
Original Source Buchacz K AIDS 1010;24:1549-59 . Image from National HIV Curriculum available at hiv.uw.edu.

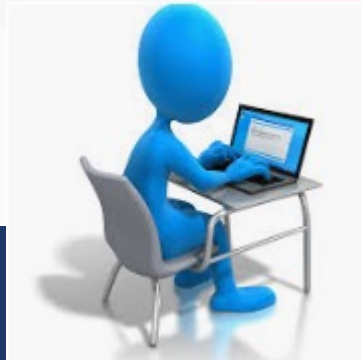
Why do we still see OIs?

- Undiagnosed or late diagnosis of HIV
- Known HIV infection with poor retention in care
- Not on stable antiretroviral therapy (ART)

DHHS Guidelines
HIV.gov







Opportunistic Infections

- Can be first presentation of HIV
- Cause morbidity and mortality
- Often preventable
  - OI Prophylaxis
  - Antiretroviral therapy (ART)
- Immune reconstitution inflammatory syndrome (IRIS)

OI Prophylaxis

Primary Prophylaxis	Prevention of first episode of disease Risk is based on CD4 count
Secondary Prophylaxis	Prevention of relapse of disease after treatment

Primary Prophylaxis

OI	Indication	Preferred
Pneumocystis Pneumonia (PCP)	CD4 < 200 CD4 < 14% If ART initiation has to be delayed, CD4 ≥ 200, but < 250 and can't monitor every 3 mos	1. TMP-SMX 1 DS tab PO daily 2. TMP-SMX 1 SS tablet daily
Toxoplasma gondii Encephalitis	Toxoplasma IgG positive with CD4 < 100	TMP-SMX 1 DS PO daily
Mycobacterium avium Complex (MAC)	CD4 < 50 • Not recommended for those who immediately start ART • Rule out active disease before starting	1. Azithromycin 1200 mg PO once weekly 2. Clarithromycin 500 mg PO BID 3. Azithromycin 600 mg PO twice weekly

DHHS. Adult and Adolescent Guidelines Table 1. Reviewed January 12 2022

When to Stop Primary Prophylaxis

OI	Indications for Discontinuing Primary Prophylaxis	Indication for Restarting Primary Prophylaxis
Pneumocystis Pneumonia (PCP)	• CD4 increased from < 200 to > 200 for > 3 mos in response to ART • Can consider when CD4 count 100-200 if HIV RNA < limit of detection for ≥ 3-6 mos	• CD4 < 100 • CD4 100-200 and HIV RNA above detection limit of assay
Toxoplasma gondii encephalitis	• CD4 > 200 for > 3 mos in response to ART • Consider when CD4 100-200 if HIV RNA < limit of detection for at least 3-6 mos	• CD4 count <100 • CD4 100-200 and HIV RNA above detection limit of assay
Mycobacterium avium Complex (MAC)	Initiation of effective ART	CD4 < 50, only if not on fully suppressive ART

DHHS. Adult and Adolescent Guidelines Table 4. Reviewed Januray 12 2022

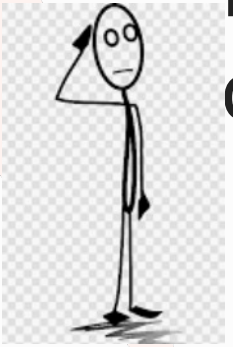
Secondary Prophylaxis

Disease	Preferred Drug	Stop
PCP	TMP/SMX (AI)	CD4 > 200 for > 3 months (AII)
Toxoplasmosis	Pyrimethamine + Sulfadiazine + Leucovorin (AI) or TMP/SMX (BII)	Completed initial therapy and CD4 > 200 for > 6 months (BI)
MAC	Clarithromycin + Ethambutol (AI) or Azithromycin + Ethambutol (AII)	Completed > 12 months therapy, asymptomatic and CD4 > 100 for > 6 months (AII)

Case Scenario 1

- Mr A is a 36 yo man admitted with fever, weight loss and productive cough for 1 month. Prior to admission, he received 2 courses of antibiotics from his PCP without improvement in his symptoms. Over the last week, he noted progressively worsening shortness of breath and now cannot walk 15 feet without stopping to catch his breath
- Epidemiology: lives in Florida, no travel, no street drug use, has male sex partners only
- CBC & CMP normal
- LDH 800 mg/dL
- Room air ABG pH 7.44 $PaCO_2$ 32 mm Hg, PaO_2 62 mm Hg, HCO_3 20 mEq/L
- What do you think is going on? How will you make a diagnosis?

Pneumo**c**ystis **P**neumonia (PCP)



- Causative organisms: *Pneumocystis jiroveci*
- Prior to effective use of ART and PCP prophylaxis, occurred in up to 80% of people with AIDS
  - Initially thought to be a protozoan, but DNA analysis demonstrated it is a **fungus**
  - Airborne
  - Species specific: PCP only affects humans

Diagnosis

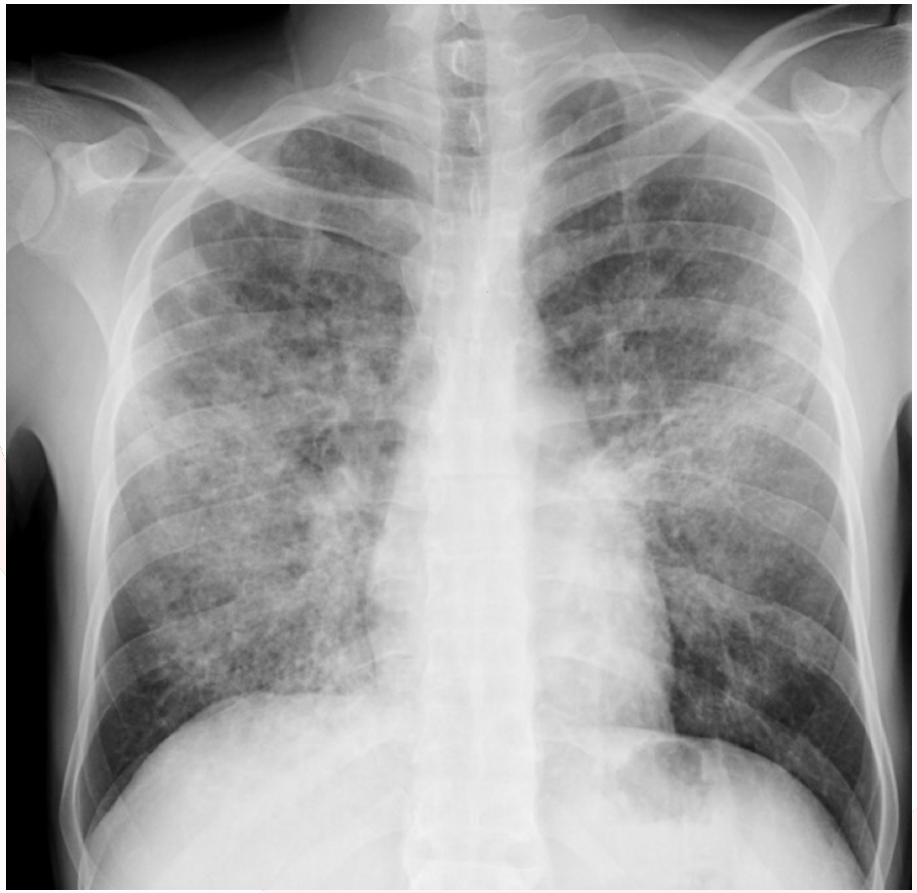
Nondefinitive

- Chest Xray
- High resolution chest CT
- Exercise pulse ox
- Labs
  - Elevated LDH (> 500 mg/dl)
  - 1,3-beta-D-glucan ≥ 80 pg/mL

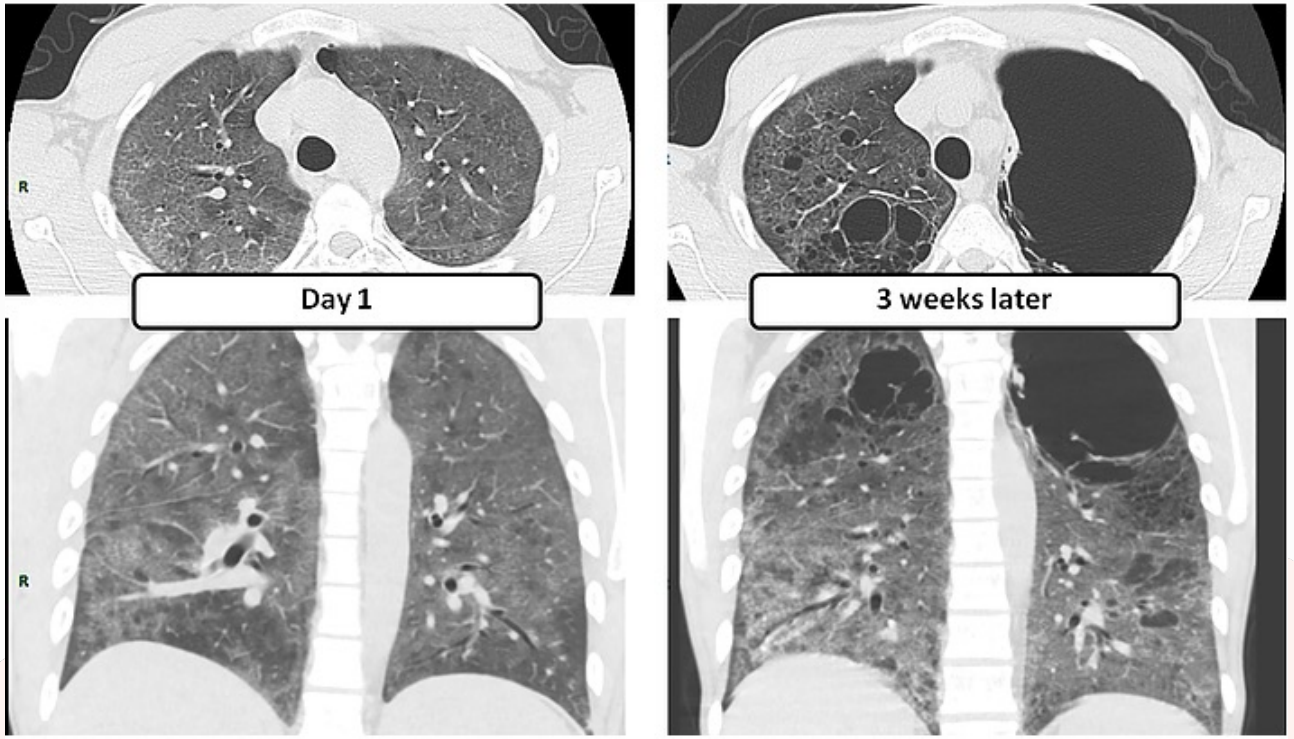
Definitive – detection of organism in resp secretions or tissue

- Induced sputum
- Bronchoscopy
- Transbronchial or open lung biopsy
- Detection of *P jiroveci* organisms in sample

Chest Imaging Suggestive of PCP



National HIV Curriculum Available at hiv.uw.edu.



Rice KM. Global Radiology CME. October 21, 2015.
Available at https://www.globalradcme.com/single-post/2015/10/21/Pneumocystis-Pneumonia-PCP-with-Pneumatoceles-1

Should Mr. A Be Admitted?

Mild to Moderate PCP

- PaO2 > 70 mm Hg
- A-a gradient < than 35
- If nontoxic appearing, can consider outpatient treatment

Moderate to Severe PCP

- Room air PO2 < 70 mm Hg
- A-a gradient ≥ 35
- Must be admitted

PCP: Treatment (mild-moderate disease)

Preferred Regimen (oral)

- TMP-SMX (high dose) (AI)

Alternative Regimens (oral)

- Dapsone + TMP (BI)
- Primaquine + clindamycin (BI)
- Atovaquone (BI)

PCP: Treatment (moderate-severe)

Preferred Regimen (AI)

- TMP-SMX (IV) + steroids
- Steroids if PaO_2 <70 mmHg at room air *or* Alveolar-arterial O_2 gradient ≥35 mm Hg
- Start ASAP and within 72 hours of PCP therapy

Alternative Regimens

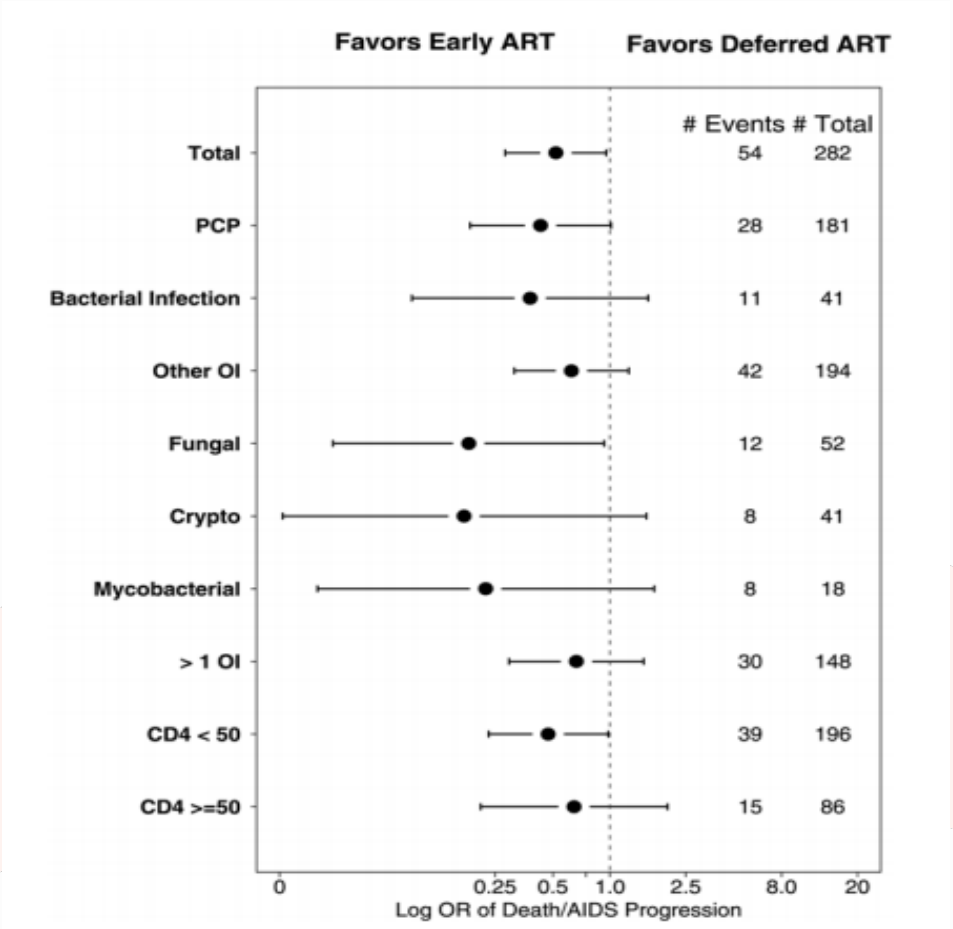
- Pentamidine (AI)
- Primaquine + clindamycin (AI)

PCP: Treatment

- After completion of 21 day treatment, start secondary prophylaxis
- Patients with PCP can be slow to improve
  - Watch out for nonadherence or IRIS-may need prolonged treatment/re-admit
- Consider this diagnosis in patient with HIV and pneumothorax
- Failure of TMP-SMX is rare, even in people who were taking it for PCP prophylaxis

Should Mr. A be started on ART? When?

- ART should be started within 2 weeks of diagnosis of PCP



Zolopa AR, et al. PloS One. 2009;4:35575.

Case Scenario 2

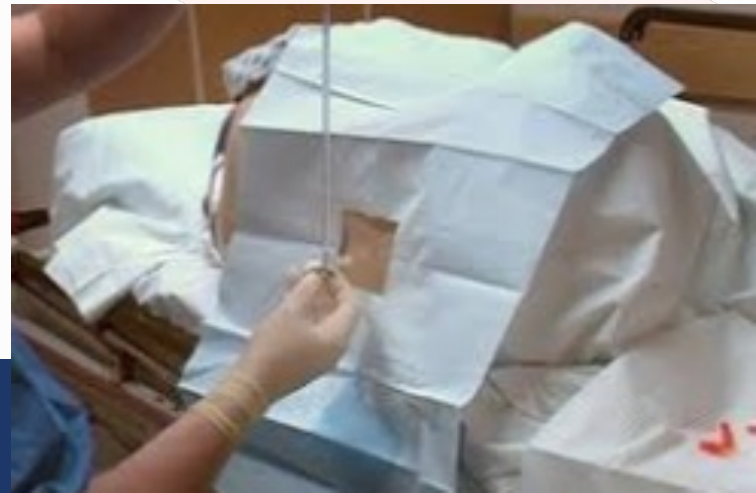
- Mr. B is a 44 year old man who arrives in the emergency room complaining of a 5 day history of headaches and new onset seizures. He is post-ictal after a witnessed seizure but can tell you he has a history of HIV and has not taken medications nor seen a healthcare provider in 9 months. There are no prior records in the health system.
- Exam T 36.7C (98.1F) HR 91 RR 16 BP 164/96
- No nuchal rigidity, negative Kernig's and Brudzinski's signs
- Exam otherwise unremarkable
- Labs: CSF WBC 102 Lymph 82% Monos 9%
- RBC 13; protein 40; glucose 63
- Opening pressure: 38 cm H_2O (> 25 cm H_2O abnormal)

Cryptococcal Meningitis

- Most common cause of meningitis in people with advanced HIV
- *Cryptococcus neoformans* > *Cryptococcus gattii*
- Hallmark is meningoencephalitis or subacute meningitis symptoms
  - Headache, fever, altered mental status
  - Classic meningitis symptoms in only 1/4 to 1/3 of patients
  - May see signs/symptoms of elevated CSF pressure
  - Approximately 25-30% of pts have a normal CSF profile
- Needs admission: lumbar puncture, IV treatment
- Prolonged treatment course (induction, consolidation, maintenance)

Mr. B – Follow-up

- CSF cryptococcal antigen 1:1024
- CSF culture: *Cryptococcus neoformans*
- Therapeutic LPs done daily and eventually a VP shunt was placed due to persistently elevated CSF pressure
- Keppra started for seizure prophylaxis



Cryptococcal Meningitis: Treatment

- Induction therapy for 2+ weeks
  - Preferred: Amphotericin B + flucytosine (5FC)
    - Preferred: liposomal formulation of amphotericin but can use other formulations
- Consolidation therapy for 8 weeks
  - Preferred: fluconazole – 800mg
- Chronic maintenance therapy
  - Preferred fluconazole – 200mg

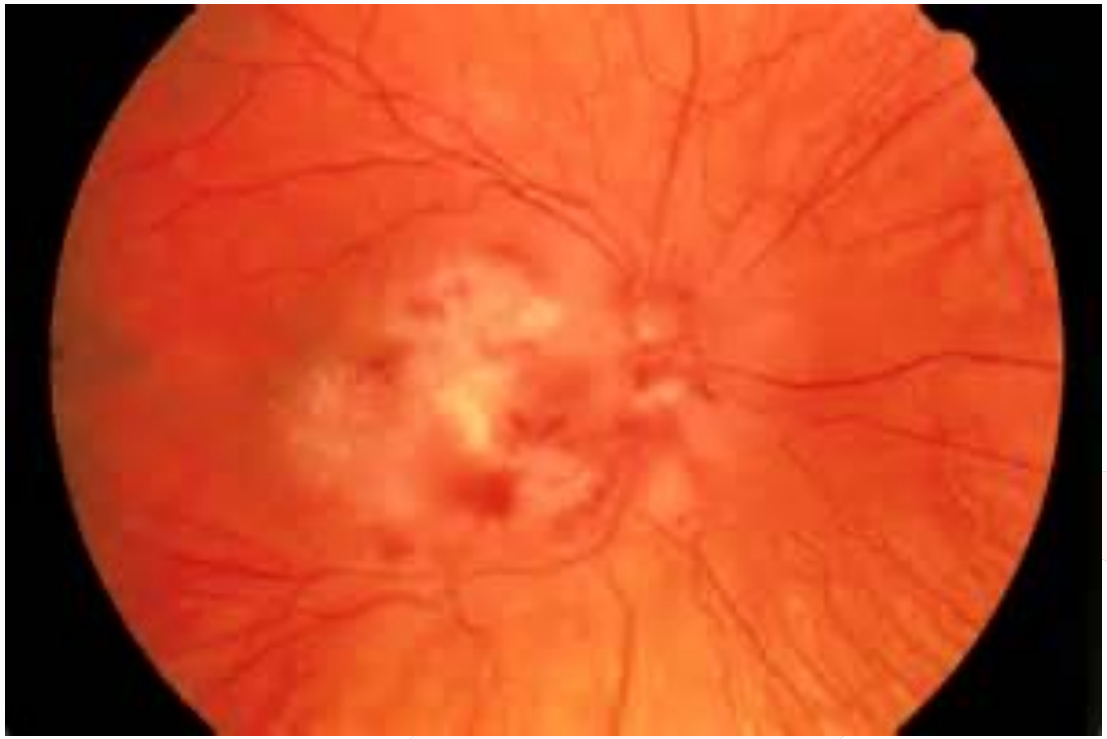
Cryptococcal Meningitis
Chronic Maintenance Therapy: Duration

- Duration (BII):
  - Completed 1 year of maintenance therapy
  - Asymptomatic
  - CD4 count ≥ 100 for ≥ 3 months and suppressed HIV RNA in response to effective ART
  - Restart maintenance if patient's CD4 drops less than 100

Case Scenario 3

- Mrs. C presents to the emergency room in rural Florida with complaints of enlarging blind spots in her vision for the last week. She has a history of HIV with loss to follow and poor adherence to ART.
- She was referred to ophthalmology and saw them one week later, but had complete vision loss by that time.

CMV Retinitis



Imagebank.asrs.org

CMV (virus)

- Double-stranded DNA virus
- CMV retinitis is most common manifestation
- Presents first in one eye (floaters, visual field defects) and then may spread to the other
- Can affect any organ, disseminate-colitis/esophagitis, encephalitis/ventriculitis, or hepatitis
- No primary prophylaxis recommended (AI)

- CMV viremia can be detected by PCR, antigen assays or culture
  - Usually but not always present in end organ disease
  - Some patients can have viremia and no end organ disease

- Needs admission: eye exam and treatment (oral vs IV/intravitreal)

CMV Retinitis: Treatment

Preferred Regimen (AI)

Intravitreal injections of ganciclovir or foscarnet (AIII)

+

Valganciclovir (high dose) for 14-21 days, then lower dosing (AI)

CMV Retinitis: Secondary Prophylaxis

Preferred Regimen (AI)

- Valganciclovir

Duration:

- CMV treatment for at least 3–6 months, lesions are inactive, with CD4 count >100 cells/mm^3 for 3 to 6 months in response to ART (AII)
- Discontinue in consultation with an ophthalmologist

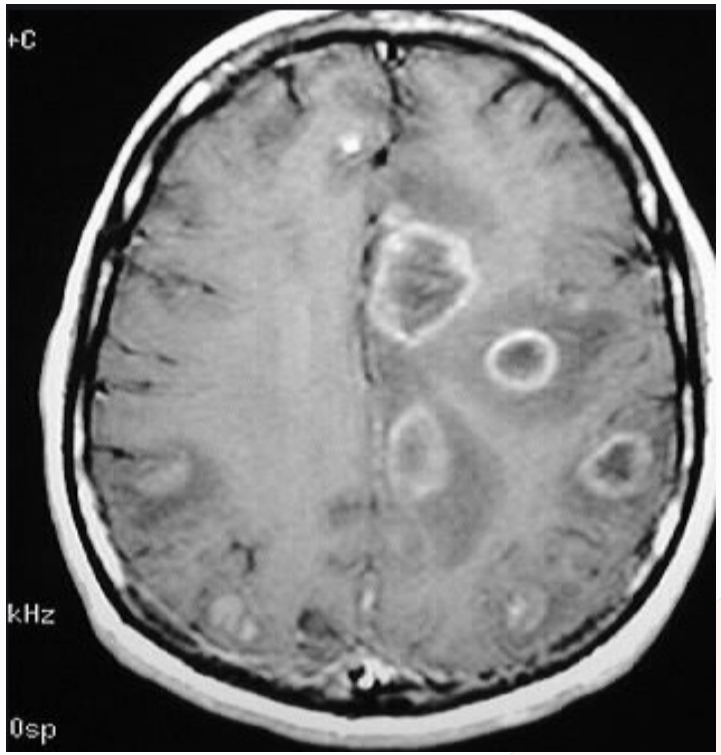
Case Scenario 4

- Ms. D is a 33 year old woman, recently diagnosed with HIV after presenting with *Toxoplasma* infection, for which she is receiving treatment. Five weeks ago you met with her to enroll her in the Ryan White case management services and she started ART shortly thereafter. Today she is here to discuss things further and you note that she is very confused and agitated.

Toxoplasma gondii Encephalitis

- Protozoan
- Disease almost always due to reactivation of latent cysts
- Prior to availability of ART, 12-month incidence of toxoplasma encephalitis was 33% in those seropositive for *T gondii* and not on prophylaxis
- Rare if CD4 > 200 – greatest risk if CD4 < 50

Toxoplasma: Brain CT



Typically multiple contrast-enhancing lesions in gray matter of cortex or basal ganglia, but can have single or no lesions

http://neuroradiologyteachingfiles.com/bfa.html

Treatment
≥ 6 weeks

Preferred Regimen (AI)

- Pyrimethamine + sulfadiazine + leucovorin

Note: if pyrimethamine is unavailable/there is a delay in obtaining it, TMP-SMX should be utilized in place of pyrimethamine-sulfadiazine (BI)

Alternative Regimen

- numerous others exist

Treatment
Chronic Maintenance

Preferred Regimen (AI)

- Pyrimethamine + sulfadiazine + leucovorin

Duration:

- completed initial therapy
- asymptomatic
- CD4 count > 200 for > 6 months (BI)

When to Start Antiretroviral Therapy in *T gondii* Encephalitis?

- No data
- Many would start ART within 2-3 weeks after diagnosis of *T gondii* encephalitis

- Should you start anticonvulsant therapy?
  - Only if patient has a seizure
  - If indicated, continue through period of acute therapy

DHHS. Adult and Adolescent Guidelines. Reviewed January 12 2022

Immune Reconstitution Inflammatory Syndrome: IRIS

- Inflammatory disease in response to a specific opportunistic pathogen weeks to months after starting ART
    1) Paradoxical IRIS: Exacerbation of partially or recently treated OI
    2) Unmasking IRIS: Inflammatory response to a previously undiagnosed OI
- Caused by enhanced/dysregulated immune response to antigens
- Greatest risk when starting ART at a high viral load and CD4 < 50
- Can be difficult to identify → diagnosis of exclusion
- Management: treat OI, continue ART, treat with anti-inflammatory if necessary (NSAIDS, steroids)

When Should ART Be Started?

Opportunistic Infection	When to start ARV's
PCP/PJP	Within 2 weeks (AI)
Cryptococcus meningitis	Between 2-10 weeks (BIII)
Toxoplasma encephalitis	Within 2-3 weeks can be up to 6 weeks (CIII)
CMV retinitis	Within 2 weeks (CIII)
Tuberculosis	Pulmonary disease and CD4 < 50 within 2 weeks after TB treatment started If CD4 > 50 (no suspected meningitis) within 8 weeks of TB therapy start
Candidiasis	No delay

CNS Disease in HIV: Differential Diagnosis

- Toxoplasma
- Lymphoma
- Cryptococcus
- Progressive multifocal leukoencephalopathy (PML)
- CMV
- Aseptic meningitis
- HIV-associated dementia
- PET and SPECT scans helpful in differentiating toxoplasmosis, PML and lymphoma

Mycobacterium avium Complex (MAC)

- Ubiquitous in the environment
- Typically seen in people with CD4 < 50
- Usually disseminated, multi-organ infection, though can be localized
- Typical symptoms: weight loss, fever, night sweats, fatigue, diarrhea and abdominal pain
- Physical finding: hepatomegaly, splenomegaly, or lymphadenopathy
- Lab abnormalities: anemia, elevated liver alkaline phosphatase
- Diagnosis: clinical signs/symptoms + isolation of MAC from cultures of blood, lymph node, bone marrow or other normally sterile tissue or body fluids

MAC: Treatment

Preferred Therapy:

- At least 2 drugs as initial therapy to prevent or delay emergence of resistance **(AI)**
  - Clarithromycin 500 mg PO twice daily **(AI)** plus ethambutol 15 mg/kg PO daily **(AI)**, *or*
  - Azithromycin 500–600 mg **(AII)** plus ethambutol 15 mg/kg PO daily **(AI)** when drug interactions or intolerance precludes the use of clarithromycin
  - **Note**: Testing of susceptibility to clarithromycin or azithromycin is recommended.

Chronic Maintenance Therapy (Secondary Prophylaxis):

- Same as treatment regimens

*Criteria for Discontinuing Chronic Maintenance Therapy **(AII)**:*

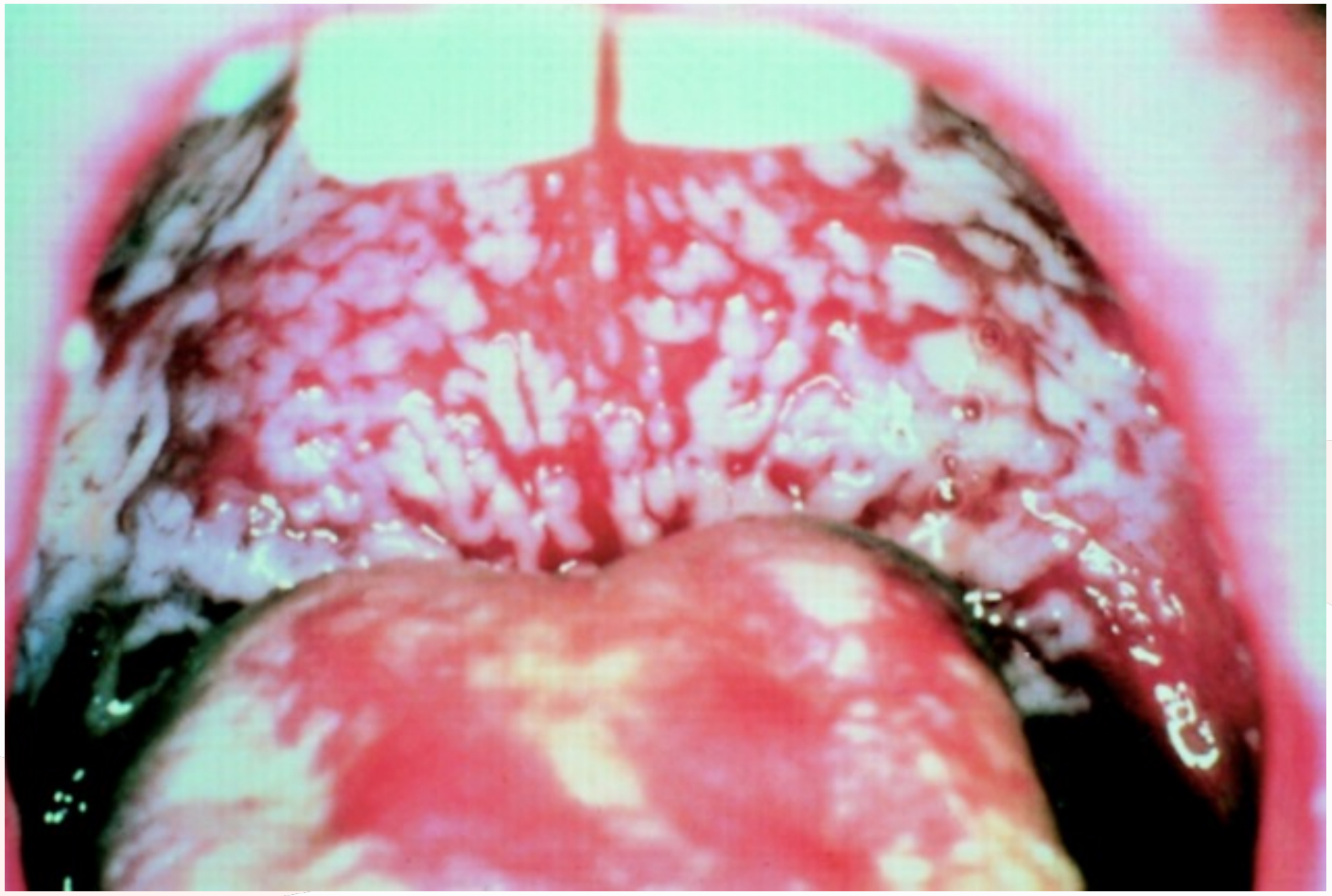
- Completed **at least** 12 months therapy, *and*
- No signs and symptoms of MAC disease, *and*
- Have sustained (>6 months) CD4 count >100 cells/mm^3 in response to ART

Indication for Restarting Secondary Prophylaxis:

- CD4 <100 cells/mm^3 **(AIII)**

DHHS. Adult and Adolescent Guidelines. Updated 02 17 2022.

Oral Candidiasis



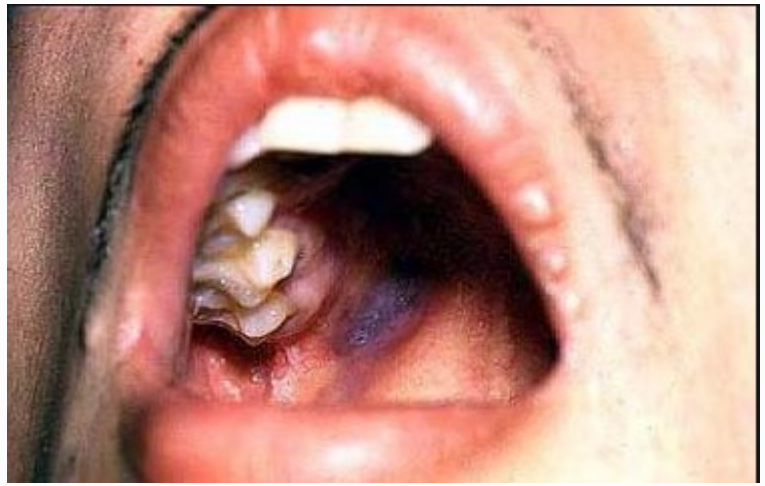
Candidiasis

- Oropharyngeal (thrush), esophageal
- Concern when CD4 < 200
- Painless, creamy white, plaque-like lesions on tongue
- Esophageal candidiasis: ‘chest pain’ or burning, pain on swallowing, nausea -> other differentials exist (CMV, HSV, aphthous ulcers)
- No routine primary prophylaxis (AIII), typically no need for chronic suppressive therapy

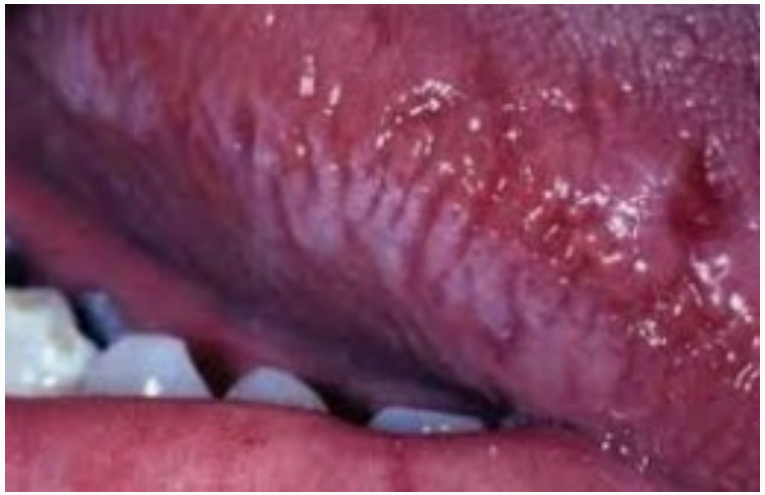
Candidiasis

- Oral
  - Preferred therapy – fluconazole 100 mg PO daily
  - Duration of therapy 7-14 days
- Esophageal candidiasis
  - Preferred therapy – fluconazole 100 mg PO or IV daily or Itraconazole oral solution 200 mg PO daily
  - Duration of therapy – 14-21 days

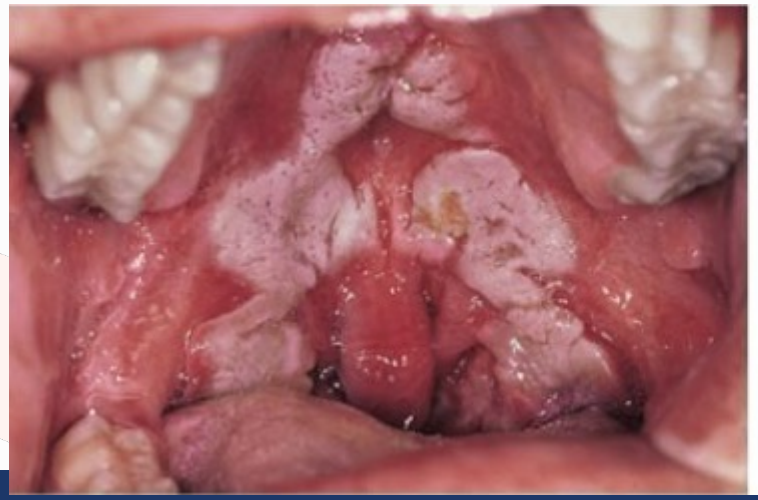
Other Oral Lesions

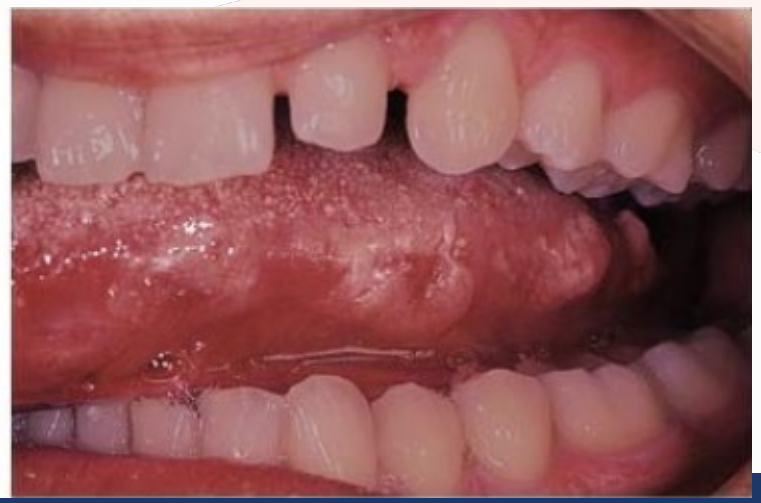


Kaposi's Sarcoma – HHV8



Oral hairy leukoplakia - EBV





Bacterial Pneumonia in HIV

- Incidence has decreased since availability of ART, but remains more common in people with HIV than those without
- Recurrent pneumonia (2 or more episodes in 1 year) is an AIDS-defining condition
- Can occur at any stage of HIV disease and at any CD4 count
- All people with HIV should receive an annual influenza vaccine

Tuberculosis: #1 OI Worldwide

- Recent transmission, reactivation
- **Annual** risk of reactivation in people with untreated latent tuberculosis infection and HIV is 3-16%
- Clinical presentation depends on degree of immunodeficiency
  - CD4 > 200 – TB limited to lungs, upper lobe fibronodular infiltrates +/- cavitation, caseating granulomas
  - CD4 < 200 – extra-pulmonary, lower/middle lobe, interstitial, military infiltrates, non-caseating granulomas

Tuberculosis

- Test for latent TB – PPD ≥ 5 mm is positive in person with HIV, rule out active disease
- Interferon gamma release assay (IGRA) – Quantiferon TB Gold Plus or T-Spot
- Significant TB exposure? Treat for latent TB regardless of PPD or IGRA
- Active TB? Look out for drug-drug interactions between TB treatment and ART

OIs: Exposures and Prevention

- Sexual- hepatitis A, B and C, Syphilis, *Chlamydia*, *Gonorrhea*
- IV drug abuse (IVDA)-Hep B, Hep C , Bacterial infections
- Environment
- Other individuals
- Animals/Pets
- Food and Water
- Travel

OIs and Adherence

- Adherence to antiretroviral therapy and OI prophylaxis predicts clinical outcomes
- Remind patients that OIs are preventable in most cases!
- Do not presume patients are taking their prophylaxis
- When asking about adherence to ART also ask about adherence to prophylactic medications

Summary

- While OIs are less common than in the past, they still occur
- Risk for OIs predicted by CD4 count
- May see multiple OIs in the same patient
- Keep a high index of suspicion for OIs in people with low adherence or known advanced HIV
- OIs can be prevented by ART and prophylaxis as well as counseling to avoid risks (see OI guidelines)

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Questions?

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Thank You.