Opportunistic Infections Associated with Human Immunodeficiency Virus Infection

Definition

- Acquired immunodeficiency syndrome (AIDS)-related opportunistic infections are defined as those infections that occur with increased frequency or severity in patients with human immunodeficiency virus (HIV) infection or AIDS.

Epidemiology

- The incidence of HIV-related opportunistic infections depends on the degree of immunosuppression and environmental exposure.
- The occurrence of specific infections in some cases is due to primary infection; in other cases, disease is the result of reactivation of latent infection.

PROSPECTIVE MONITORING

- The CD4+ T-cell count
- HIV viral load
- Clinical findings

Microbiology

- The constellation of infections that characterize AIDS is unique: Pneumocystis pneumonia, Toxoplasma encephalitis, cytomegaloviral retinitis, pneumococcal pneumonia, disseminated Mycobacterium avium complex, cryptosporidiosis, cryptococcal meningitis, and Mycobacterium tuberculosis infection. The occurrence of these infections individually or in a cluster should prompt consideration of underlying HIV infection/AIDS in any patient without a clear predisposing immunodeficiency.

- The organisms that cause HIV-related opportunistic infections include bacteria, fungi, viruses, and protozoa. Some are transmitted person to person, whereas others are present in certain environmental niches.

Diagnosis

- Given the broad range of pathogens that can cause infectious syndromes in patients with HIV infection/AIDS, and the potential toxicities of therapeutic agents, specific microbiologic diagnoses should be established when possible. AIDS-related opportunistic infections are diagnosed by a wide variety of techniques, including bacterial and fungal and viral culture, serum or body fluid antigen assays or polymerase chain reaction assays, colorimetric and immunofluorescent stain of secretions or tissue, and histology.

MANAGEMENT OF ANTIRETROVIRAL THERAPY FOR PATIENTS WITH ACUTE OPPORTUNISTIC INFECTION

GENERAL PRINCIPLES OF MANAGEMENT:

- Primary Px
- Prompt Dx
- effective ART
- Reevaluation
- Secondary Px
- Drug interactions
- IRIS

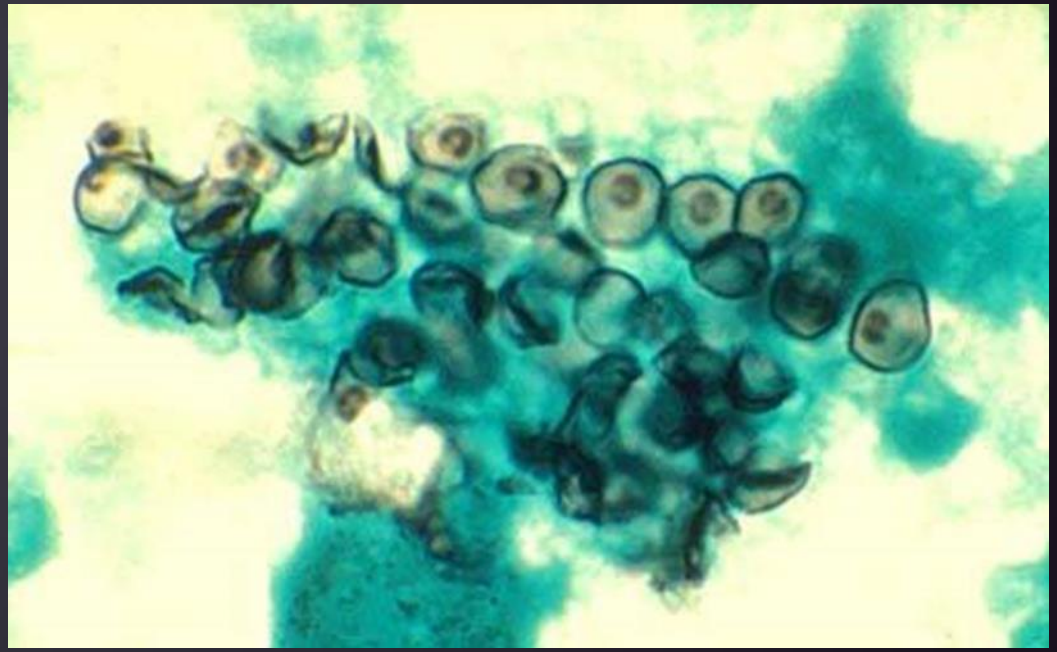
PCP

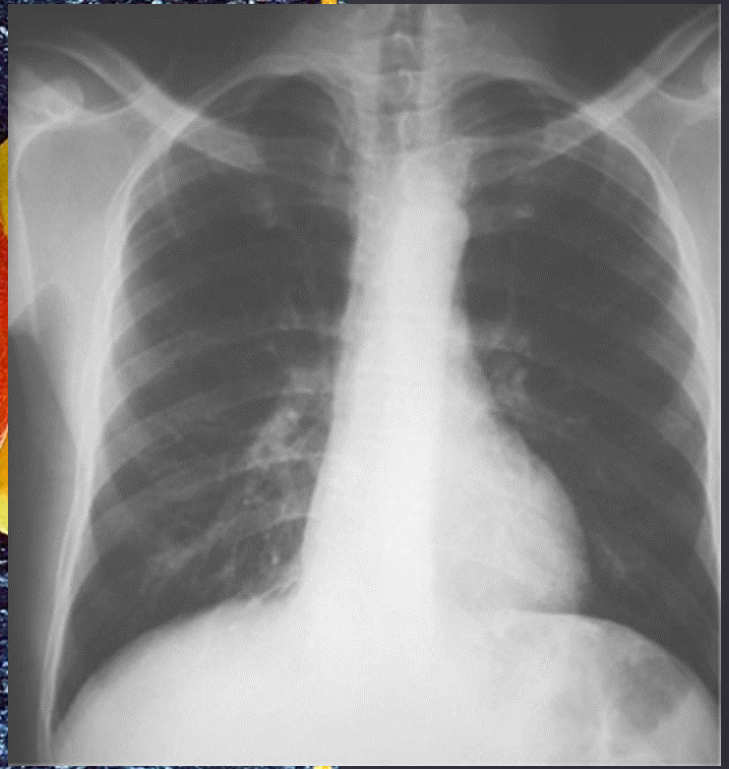
- PCP was the clinical manifestation that originally suggested to clinicians that a new syndrome, AIDS, was occurring in patients who appeared to be previously healthy.

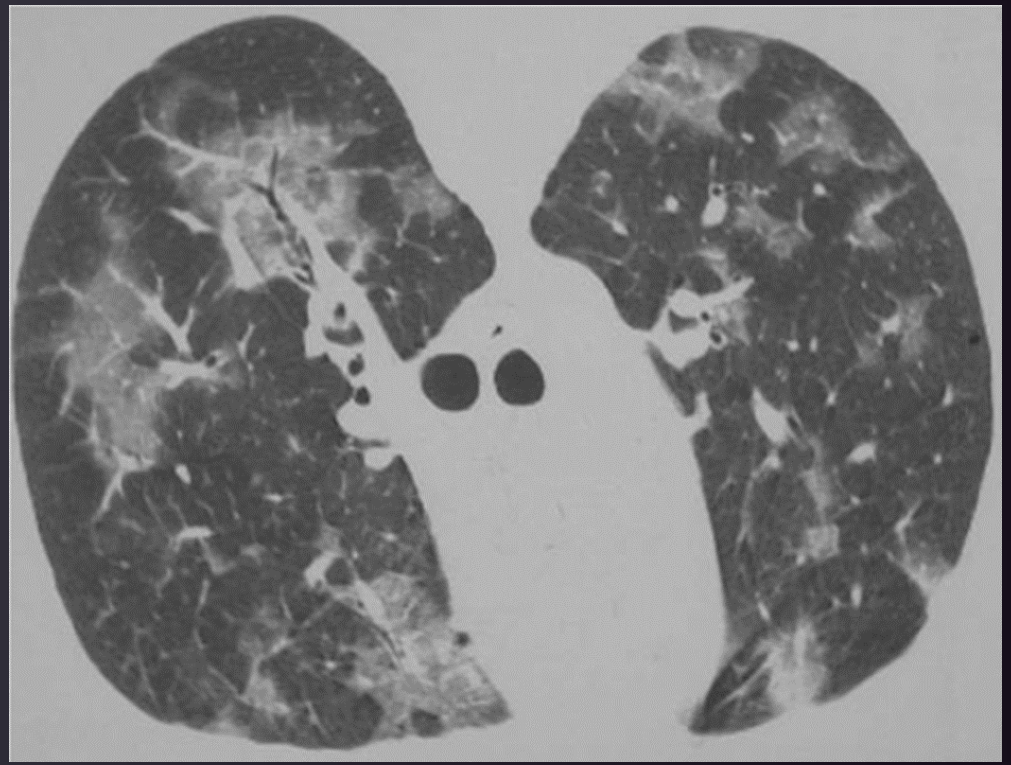
- Pneumocystis causes disease almost exclusively in the lungs
- Chest tightness or exercise intolerance
- Infiltrates in chest radiographs
- Hypoxemia in ABG

Diagnosis:

- visualization of Pneumocystis by colorimetric or immunofluorescent stain in sputum, bronchoalveolar lavage, or tissue is definitive for diagnosis of PCP
- Nucleic acid detection systems for PCP that use oral washes, gargles, sputum, or bronchoalveolar lavage
- β1-glucan detection in serum or bronchoalveolar lavage is not sufficiently sensitive or specific







Poor prognosis:

- an alveolar-arterial gradient greater than 30 mm Hg
- a severely abnormal chest radiograph
- a large number of organisms detected on lavage or biopsy
- comorbid conditions
- Delayed treatment

Primary prophylaxis

Pneumocystis pneumonia (PCP)	CD4 count <200 cells/mm^3, *or* oropharyngeal candidiasis, *or* CD4 <14%, or history of AIDS-defining illness, *or* CD4 count >200 but <250 cells/mm^3 if monitoring CD4 cell count every 3 mo is not possible *Note:* Patients who are receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis.	TMP-SMX 1 DS tablet PO daily, *or* TMP-SMX 1 SS tablet PO daily	TMP-SMX 1 DS tablet PO three times a week, *or* Dapsone 100 mg PO daily or 50 mg PO bid, *or* Dapsone 50 mg PO daily + pyrimethamine 50 mg + leucovorin 25 mg PO weekly, *or* Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg PO weekly; *or* Aerosolized pentamidine 300 mg via Respirgard II nebulizer every month, *or* Atovaquone 1500 mg PO daily, *or* Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg PO daily
Toxoplasma gondii encephalitis	*Toxoplasma* IgG-positive patients with CD4 count <100 cells/mm^3 Seronegative patients receiving PCP prophylaxis not active against toxoplasmosis should have *Toxoplasma* serology retested if CD4 count declines to <100 cells/mm^3. Prophylaxis should be initiated if seroconversion occurred. *Note:* All regimens recommended for primary prophylaxis against toxoplasmosis are also effective as PCP prophylaxis.	TMP-SMX 1 DS tablet PO daily	TMP-SMX 1 DS tablet PO three times a week, *or* TMP-SMX 1 SS tablet PO daily, *or* Dapsone 50 mg PO daily + pyrimethamine 50 mg + leucovorin 25 mg PO weekly, *or* Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg PO weekly; *or* Atovaquone 1500 mg PO daily; *or* Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg PO daily
Mycobacterium tuberculosis infection (i.e., treatment of LTBI)	Positive screening test for LTBI, with no evidence of active TB, and no prior treatment for active TB or LTBI, *or* Close contact with a person with infectious TB, with no evidence of active TB, regardless of screening test results.	INH 300 mg + pyridoxine 25 mg PO daily × 9 mo, *or* INH 900 mg PO twice weekly (by DOT) + pyridoxine 25 mg PO daily × 9 mo.	Rifampin 600 mg PO daily × 4 mo, *or* Rifabutin (dose adjusted based on concomitant ART) × 4 mo. For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts or public health authorities.
Disseminated *Mycobacterium avium* complex (MAC) di…	CD4 count <50 cells/mm^3 after ruling out active disseminated MAC disease based on clinical assessment.	Azithromycin 1200 mg PO once weekly, *or* Clarithromycin 500 mg PO bid, *or* Azithromycin 600 mg PO twice weekly	Rifabutin (dose adjusted based on concomitant ART); rule out active TB before starting rifabutin.

treatment

Pneumocystis pneumonia (PCP)	Patients who develop PCP despite TMP-SMX prophylaxis can usually be treated with standard doses of TMP-SMX Duration of PCP treatment: 21 days		Indications for adjunctive corticosteroids: PaO_2 <70 mm Hg at room air, *or* Alveolar-arterial O_2 gradient >35 mm Hg Prednisone doses (beginning as early as possible and within 72 hr of PCP therapy): Days 1-5: 40 mg PO bid Days 6-10: 40 mg PO daily Days 11-21: 20 mg PO daily IV methylprednisolone can be administered as 75% of prednisone dose. Benefit of corticosteroid if started after 72 hr of treatment is unknown, but some clinicians will use it for moderate-to-severe PCP. Whenever possible, patients should be tested for G6PD before use of dapsone or primaquine. Alternative therapy should be used in patients found to have G6PD deficiency. Patients who are receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis. If TMP-SMX is discontinued because of a mild adverse reaction, reinstitution should be considered after the reaction resolves. The dose can be increased gradually (desensitization), reduced, or the frequency modified. TMP-SMX should be permanently discontinued in patients with possible or definite Stevens-Johnson syndrome or toxic epidermal necrosis.
	For moderate-to-severe PCP: TMP-SMX: (TMP 15-20 mg and SMX 75-100 mg)/kg/day IV given q6h or q8h; may switch to PO after clinical improvement	For moderate-to-severe PCP: Pentamidine 4 mg/kg IV daily infused over ≥60 min; can reduce dose to 3 mg/kg IV daily because of toxicities, *or* Primaquine 30 mg (base) PO daily + clindamycin 600 mg q6h IV, *or* 900 mg IV q8h, *or* clindamycin 300 mg PO q6h, *or* 450 mg PO q8h	
	For mild-to-moderate PCP: TMP-SMX: (TMP 15-20 mg and SMX 75-100 mg)/kg/day, given PO in three divided doses, *or* TMP-SMX: (160 mg/800 mg or DS) 2 tablets PO tid	For mild-to-moderate PCP: Dapsone 100 mg PO daily + TMP 5 mg/kg PO tid, *or* Primaquine 30 mg (base) PO daily + clindamycin 300 mg PO q6h, *or* 450 mg PO q8h, *or* Atovaquone 750 mg PO bid with food	
	Secondary prophylaxis, after completion of PCP treatment: TMP-SMX DS: 1 tablet PO daily *or* TMP-SMX (80 mg/400 mg or SS): 1 tablet PO daily	Secondary prophylaxis, after completion of PCP treatment: TMP-SMX DS: 1 tablet PO three times a week, *or* Dapsone 100 mg PO daily, *or* Dapsone 50 mg PO daily + pyrimethamine 50 mg + leucovorin 25 mg PO weekly, *or* Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg PO weekly, *or* Aerosolized pentamidine 300 mg monthly via Respirgard II nebulizer, *or* Atovaquone 1500 mg PO daily, *or* Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg PO daily	

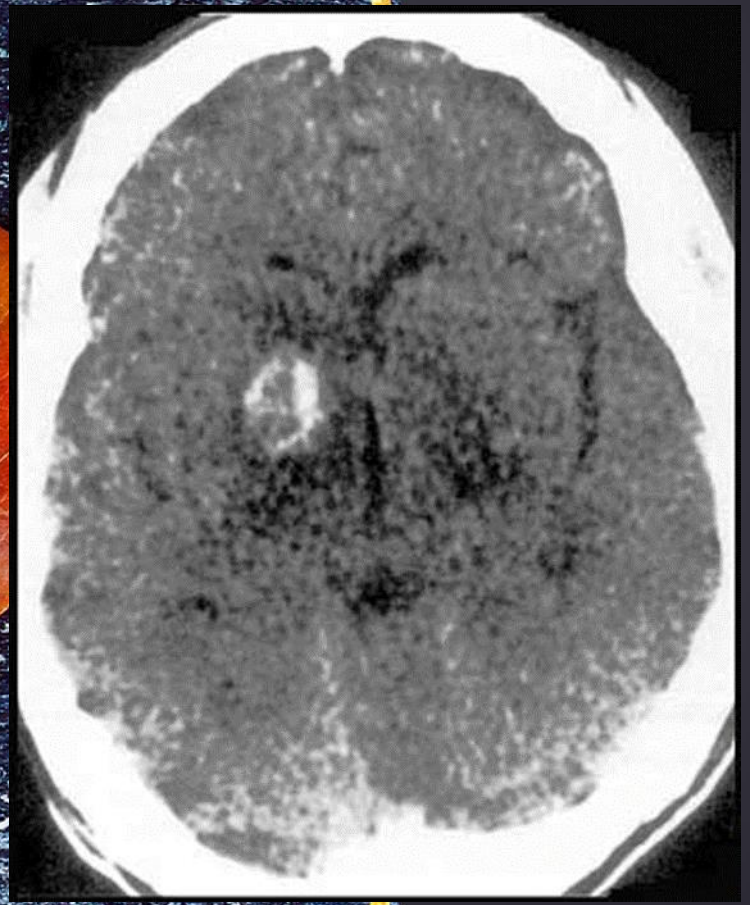
Indications for Discontinuing and Restarting Opportunistic Infection Prophylaxis

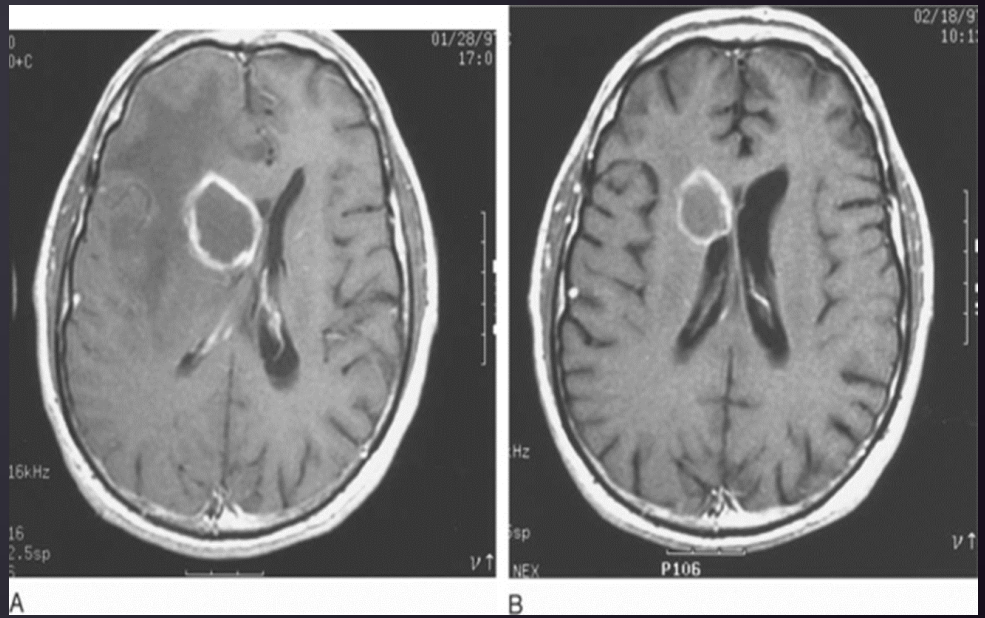
OPPORTUNISTIC INFECTION	INDICATION FOR DISCONTINUING PRIMARY PROPHYLAXIS	INDICATION FOR RESTARTING PRIMARY PROPHYLAXIS	INDICATION FOR DISCONTINUING SECONDARY PROPHYLAXIS/ CHRONIC MAINTENANCE THERAPY	INDICATION FOR RESTARTING SECONDARY PROPHYLAXIS/CHRONIC MAINTENANCE
Pneumocystis pneumonia	CD4 count increased from <200 to >200 cells/mm^3 for >3 mo in response to ART	CD4 count <200 cells/mm^3	CD4 count increased from <200 cells/mm^3 to >200 cells/mm^3 for >3 mo in response to ART. If PCP was diagnosed when CD4 count was >200 cells/mm^3, continue prophylaxis for life regardless of CD4 count rise in response to ART.	CD4 count <200 cells/mm^3, *or* If PCP recurred at CD4 count >200 cells/mm^3, prophylaxis should be continued for life.
Toxoplasma gondii encephalitis (TE)	CD4 count increased to >200 cells/mm^3 for >3 mo in response to ART	CD4 count <100 to 200 cells/mm^3	Successfully completed initial therapy, remain free of signs and symptoms of TE, and CD4 count >200 cells/mm^3 for >6 mo in response to ART.	CD4 count <200 cells/mm^3
Microsporidiosis	Not applicable	Not applicable	No signs and symptoms of nonocular or ocular microsporidiosis and CD4 count >200 cells/mm^3 for >6 mo in response to ART.	No recommendation
Disseminated *Mycobacterium avium* complex disease	CD4 count >100 cells/mm^3 for ≥3 mo in response to ART	CD4 count <50 cells/mm^3	<u>If the following criteria are fulfilled:</u> Completed ≥12 mo of therapy, and No signs and symptoms of MAC disease, and Have sustained (>6 mo) CD4 count >100 cells/mm^3in response to ART	CD4 count <100 cells/mm^3
Salmonellosis	Not applicable	Not applicable	Resolution of *Salmonella* infection and after response to ART with sustained viral suppression and CD4 counts >200 cells/mm^3	No recommendation
Cryptococcal meningitis	Not applicable	Not applicable	<u>If the following criteria are fulfilled:</u> Completed initial (induction and consolidation) therapy, and Received at least 1 yr of maintenance therapy, and Remain asymptomatic of cryptococcal infection, and CD4 count ≥100 cells/mm^3 for >3 mo and with suppressed plasma HIV RNA in response to	CD4 count <100 cells/mm^3

Toxoplasma gondii

- primarily by reactivation of latent disease rather than by primary infection
- manifests most often as cerebral disease presenting as fever, headache, confusion, motor defects, and seizures
- Retinochoroiditis, pneumonitis, disseminated disease, and a sepsis-like syndrome, less frequent.

- If an HIV-infected patient with a CD4+ T-cell count of less than 100 cells/mm3 presents with a space-occupying cerebral lesion that involves gray matter, the differential diagnosis should focus on two entities: toxoplasmosis and lymphoma.

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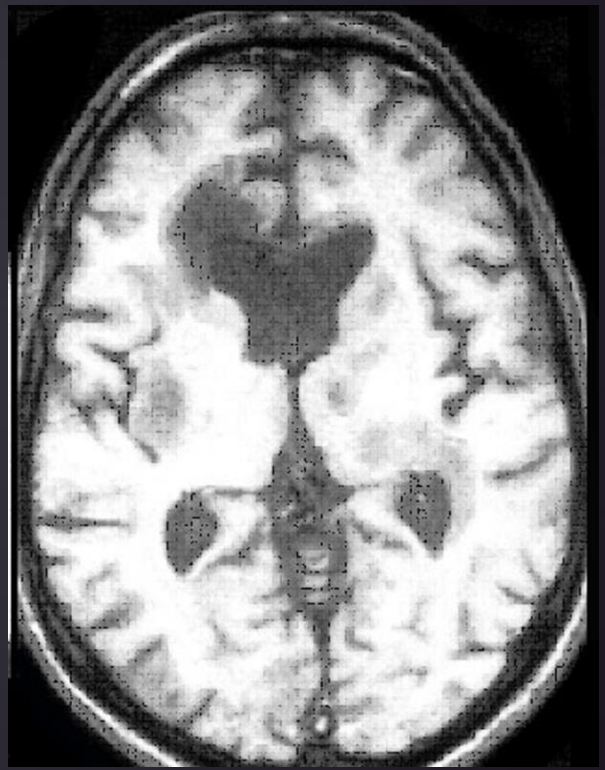
Toxoplasma gondii encephalitis	Treatment of acute infection: Pyrimethamine 200 mg PO 1 time, followed by weight-based therapy: If <60 kg, pyrimethamine 50 mg PO once daily + sulfadiazine 1000 mg PO q6h + leucovorin 10-25 mg PO once daily If ≥60 kg, pyrimethamine 75 mg PO once daily + sulfadiazine 1500 mg PO q6h + leucovorin 10-25 mg PO once daily Leucovorin dose can be increased to 50 mg daily or bid. Duration for acute therapy: At least 6 wk; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 wk Chronic maintenance therapy: Pyrimethamine 25-50 mg PO daily + sulfadiazine 2000-4000 mg PO daily (in two to four divided doses) + leucovorin 10-25 mg PO daily	Treatment of acute infection: Pyrimethamine (leucovorin)* + clindamycin 600 mg IV or PO q6h, *or* TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) IV or PO bid, *or* Atovaquone 1500 mg PO bid with food + pyrimethamine (leucovorin), *or* Atovaquone 1500 mg PO bid with food + sulfadiazine 1000-1500 mg PO q6h (weight-based dosing, as in preferred therapy), *or* Atovaquone 1500 mg PO bid with food, *or* Pyrimethamine (leucovorin)* + azithromycin 900-1200 mg PO daily Chronic maintenance therapy: Clindamycin 600 mg PO q8h + (pyrimethamine 25-50 mg + leucovorin 10-25 mg) PO daily, *or* TMP-SMX DS 1 tablet bid, *or* Atovaquone 750-1500 mg PO bid + (pyrimethamine 25 mg + leucovorin 10 mg) PO daily, *or* Atovaquone 750-1500 mg PO bid + sulfadiazine 2000-4000 mg PO daily (in two to four divided doses), *or* Atovaquone 750-1500 mg PO bid with food	Adjunctive corticosteroids (e.g., dexamethasone) should only be administered when clinically indicated to treat mass effect associated with focal lesions or associated edema; discontinue as soon as clinically feasible. Anticonvulsants should be administered to patients with a history of seizures and continued through acute treatment but should not be used as seizure prophylaxis. If clindamycin is used in place of sulfadiazine, additional therapy must be added to prevent PCP.

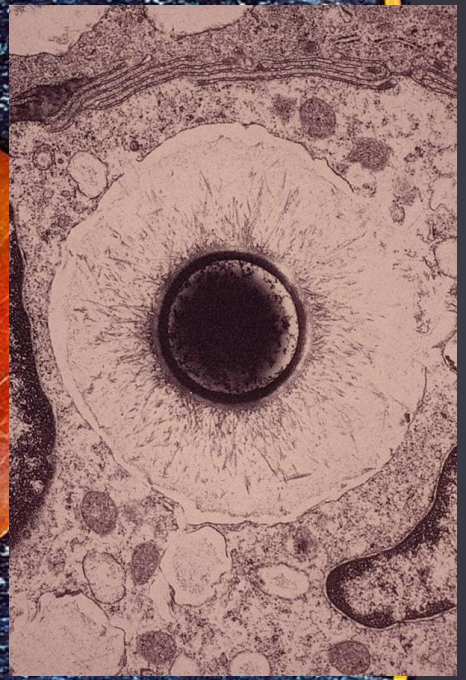
Cytomegalovirus

CMV retinitis

- CD4+ T-cell counts less than 50 cells/mm3
- Rapidly damage the macula and optic disk , ultimately blindness
- Diagnosis :clinical



Cytomegalovirus (CMV) disease	CMV retinitis: *Induction therapy for immediate sight-threatening lesions (adjacent to the optic nerve or fovea):* *Consult ophthalmologist because ganciclovir implant no longer available:* Ganciclovir 5 mg/kg IV q12h for 14-21 days followed by valganciclovir 900 mg PO bid *For small peripheral lesions:* Valganciclovir 900 mg PO bid for 14-21 days One dose of intravitreal ganciclovir can be administered immediately after diagnosis until steady-state plasma ganciclovir concentration is achieved with oral valganciclovir. Chronic maintenance (secondary prophylaxis): Valganciclovir 900 mg PO daily (for small peripheral lesion)	CMV retinitis: *Induction therapy:* Ganciclovir 5 mg/kg IV q12h for 14-21 days, *or* Foscarnet 90 mg/kg IV q12h or 60 mg q8h for 14-21 days, *or* Cidofovir 5 mg/kg/wk IV for 2 wk; saline hydration before and after therapy and probenecid, 2 g PO 3 hr before dose, followed by 1 g PO 2 hr and 8 hr after the dose (total of 4 g). (*Note:* This regimen should be avoided in patients with sulfa allergy because of cross-hypersensitivity with probenecid.) Chronic maintenance (secondary prophylaxis): Ganciclovir 5 mg/kg IV five to seven times weekly, *or* Foscarnet 90-120 mg/kg IV once daily, *or* Cidofovir 5 mg/kg IV every other week with saline hydration and probenecid as above	The choice of therapy for CMV retinitis should be individualized, based on location and severity of the lesions, level of immunosuppression, and other factors (e.g., concomitant medications and ability to adhere to treatment). The choice of chronic maintenance therapy (route of administration and drug choices) should be made in consultation with an ophthalmologist. Considerations should include the anatomic location of the retinal lesion, vision in the contralateral eye, the patients' immunologic and virologic status and response to ART. Patients with CMV retinitis who discontinue maintenance therapy should undergo regular eye examinations (optimally every 3 mo) for early detection of relapse IRU, and then annually after immune reconstitution. IRU may develop in the setting of immune reconstitution. Treatment of IRU: Periocular corticosteroid or short courses of systemic corticosteroid. Initial therapy in patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include initiation or optimization of ART.

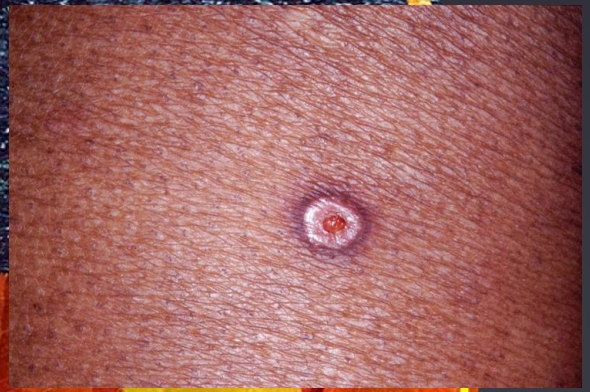


Cryptococcus neoformans

- Meningitis is the most frequent manifestation of cryptococcosis in HIV-infected patients
- fever, headache, neck stiffness, or photophobia
- In CD4+ T-cell counts less than 50 cells/mm
- Pulmonary or cutaneous manifestations
- Diagnosis: elevated protein levels and numbers of mononuclear cells and decreased glucose concentration in CSF
- CSF and serum cryptococcal antigen tests

Cryptococcosis	Cryptococcal meningitis: *Induction therapy (for at least 2 wk, followed by consolidation therapy):* Liposomal amphotericin B 3-4 mg/kg IV daily + flucytosine 25 mg/kg PO qid (*Note:* flucytosine dose should be adjusted in patients with renal dysfunction.)	Cryptococcal meningitis: *Induction therapy (for at least 2 wk, followed by consolidation therapy):* Amphotericin B deoxycholate 0.7 mg/kg IV daily + flucytosine 25 mg/kg PO qid, *or* Amphotericin B lipid complex 5 mg/kg IV daily + flucytosine 25 mg/kg PO qid, *or* Liposomal amphotericin B 3-4 mg/kg IV daily + fluconazole 800 mg PO or IV daily, *or* Amphotericin B deoxycholate 0.7 mg/kg IV daily + fluconazole 800 mg PO or IV daily, *or* Fluconazole 400-800 mg PO or IV daily + flucytosine 25 mg/kg PO qid, *or* Fluconazole 1200 mg PO or IV daily	Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF and decreased risk for subsequent relapse. Patients receiving flucytosine should have either blood levels monitored (peak level 2 hr after dose should be 30-80 μg/mL) or close monitoring of blood cell counts for development of cytopenia. Dosage should be adjusted in patients with renal insufficiency. Opening pressure should always be measured when an LP is performed. Repeated LPs or CSF shunting are essential to effectively manage increased intracranial pressure. Corticosteroids and mannitol are ineffective in reducing ICP and are *not* recommended. Some specialists recommend a brief course of corticosteroid for management of severe IRIS symptoms.
	Consolidation therapy (for at least 8 wk followed by maintenance therapy): Fluconazole 400 mg PO (or IV) daily	*Consolidation therapy (for at least 8 wk followed by maintenance therapy):* Itraconazole 200 mg PO bid for 8 wk—less effective than fluconazole	
	Maintenance therapy: Fluconazole 200 mg PO daily for at least 12 mo	*Maintenance therapy:* No alternative therapy recommendation	
	For non-CNS, extrapulmonary cryptococcosis and diffuse pulmonary disease: Treatment same as for cryptococcal meningitis Non-CNS cryptococcosis with mild-to-moderate symptoms and focal pulmonary infiltrates: Fluconazole, 400 mg PO daily for 12 mo		

Mycobacterium avium Complex



a systemic process characterized by fever, weight loss, elevated serum alkaline phosphatase levels, and substantial anemia.312-314 Wasting, diarrhea, or lymphadenopathy may be seen.

- DIAGNOSIS: blood culture or by biopsy of affected tissue
- Culture of organisms from respiratory secretions, stool, or urine does not establish the presence of invasive disease or the need for therapy.

Disseminated *Mycobacterium avium* complex (MAC) disease	<u>At least two drugs as initial therapy with:</u> Clarithromycin 500 mg PO bid + ethambutol 15 mg/kg PO daily, *or* Azithromycin 500-600 mg + ethambutol 15 mg/kg PO daily if drug interaction or intolerance precludes the use of clarithromycin *Duration:* At least 12 mo of therapy, can discontinue if no signs and symptoms of MAC disease and sustained (>6 mo) CD4 count >100 cells/mm^3 in response to ART	Addition of a third or fourth drug should be considered for patients with advanced immunosuppression (CD4 counts <50 cells/mm^3), high mycobacterial loads (>2 log CFU/mL of blood), or in the absence of effective ART. <u>Third or fourth drug options may include:</u> RFB 300 mg PO daily (dosage adjustment may be necessary based on drug interactions), Amikacin 10-15 mg/kg IV daily or streptomycin 1 g IV or IM daily, *or* Moxifloxacin 400 mg PO daily or levofloxacin 500 mg PO daily	Testing of susceptibility to clarithromycin and azithromycin is recommended. NSAIDs can be used for patients who experience moderate to severe symptoms attributed to IRIS. If IRIS symptoms persist, short-term (4-8 wk) systemic corticosteroids (equivalent to 20-40 mg prednisone) can be used.

Thank you