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Opportunistic Infections (OIs) in HIV/AIDS

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This resource summarizes the guidelines for prevention and treatment of selected opportunistic infections (OIs). A table is provided that summarizes available dosage forms and food requirements for agents used in the prevention and treatment of OIs. Unless otherwise indicated, information adapted from Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at *www.aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf*. Accessed February 5, 2015. Referred to as the "OI Guidelines" throughout resource. See OI Guidelines (page A-5) for Rating scheme/level of evidence definitions *(e.g., AI, BI, CI, etc.)* and more detailed information regarding the prevention and treatment of OIs.

Preferred OI Primary Prophylaxis

NOTE: *See Alternative OI Primary Prophylaxis section for alternative regimens. Routine primary prophylaxis is not recommended for other OIs.* See specific OIs for discussion.

Indication	Infection	Preferred Regimen
CD4 count < 200 cells/mm³ (AI) **or** % CD4 < 14% (BII) **or** oropharyngeal candidiasis (AII)[1]	*Pneumocystis jirovecii* pneumonia (PCP)	TMP-SMX 1 DS po once daily[2] (AI) **or** TMP-SMX 1 SS po once daily[2] (AI)
CD4 count < 100 cells/mm³ and toxoplasma IgG positive (AII)[3]	*Toxoplasma gondii* encephalitis	TMP-SMX 1 DS po once daily[2] (AII)
CD4 count < 50 cells/mm³ - after ruling out disseminated active MAC infection (AI)	Disseminated *Mycobacterium avium* complex (MAC) disease	Azithromycin 1200 mg po once weekly (AI) **or** clarithromycin 500 mg po bid (AI) **or** azithromycin 600 mg po twice weekly (BIII)

1. Additional indications: history of AIDS-defining illness (BII), CD4 count > 200 and < 250 if CD4 count monitoring every 3 months is not possible (BII).
2. TMP-SMX DS once daily also confers protection against toxoplasmosis and many respiratory bacterial infections; lower dose also likely confers protection.
3. Retest Toxo IgG status if CD4 count declines to < 100 and patient (pt) is receiving PCP prophylaxis not active versus toxoplasmosis (e.g., dapsone) (CIII).

The information contained in this publication is intended for medical professionals, as a quick reference to the national guidelines. This resource does not replace nor represent the comprehensive nature of the published guidelines. Recognizing the rapid changes that occur in this field, clinicians are encouraged to consult with their local experts or research the literature for the most up-to-date information to assist with individual treatment decisions for their patient. If your patient should experience a serious adverse event, please report the event to the FDA (*www.fda.gov/Safety/MedWatch/HowToReport/default.htm*) to help increase patient safety.

Visit *www.FCAETC.org/treatment* for the most up-to-date version of this resource.

Alternative OI Primary Prophylaxis

PCP (Alternatives):

NOTE: Use of pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis does not require additional prophylaxis for PCP (AII)

- TMP-SMX 1 DS po 3 times per week (BI) **or**
- Dapsone[4] 100 mg po once daily or 50 mg po bid (BI)[5] **or**
- Dapsone[4] 50 mg po once daily + (pyrimethamine 50 mg + leucovorin 25 mg) po once weekly (BI) **or**
- (Dapsone[4] 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) po once weekly (BI) **or**
- Aerosolized pentamidine 300 mg once monthly via Respirgard II® nebulizer (BI)[5] **or**
- Atovaquone 1500 mg po once daily (BI)
- (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) po once daily (CIII)

Toxoplasmosis (Alternatives):

- TMP-SMX 1 DS po 3 times per week (BIII) **or**
- TMP-SMX 1 SS po once daily (BIII) **or**
- Dapsone[4] 50 mg po once daily + (pyrimethamine 50 mg + leucovorin 25 mg) po once weekly (BI) **or**
- (Dapsone[4] 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) po once weekly (BI) **or**
- Atovaquone 1500 mg po once daily (CIII)
- (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) po once daily (CIII)

Disseminated MAC (Alternatives):

- Rifabutin 300 mg po once daily (BI)
  NOTE: Active TB should be ruled out before starting; interactions with many antiretrovirals (ARVs), may require dosage adjustments.[6]

4. Whenever possible, pts should be tested for G6PD deficiency before giving dapsone or primaquine. Alternative agent should be used if the pt is found to have G6PD deficiency.
5. Aerosolized pentamidine or dapsone (without pyrimethamine) should not be used for PCP prophylaxis in pts who are seropositive for *Toxoplasma gondii*.
6. Please refer to Table 5 of the OI Guidelines and www.hiv-druginteractions.org for dosing when used with ARVs.

Stopping Primary Prophylaxis

- **PCP:** CD4 count > 200 for > 3 months in response to antiretroviral therapy (ART) (AI), reinitiate if CD4 count falls to < 200 (AIII)
- **Toxoplasmosis:** CD4 count > 200 for > 3 months in response to ART (AI), reinitiate if CD4 count falls to < 100-200 (AIII)
- **MAC:** CD4 count > 100 for ≥ 3 months in response to ART (AI), reininitiate if CD4 count falls to < 50 (AIII)

Initiation of Antiretroviral Therapy (ART) With OIs

Immune Reconstitution Inflammatory Syndrome (IRIS) – an inflammatory reaction following improved immune function after ART initiation
- Paradoxical IRIS- an exacerbation of the acute OI diagnosed prior to ART initiation
- Unmasking IRIS- new clinical presentation of OI recognized after ART initiation. Variable onset, usually 2-4 weeks after ART initiation, most often self-limiting, but can be life-threatening.
- See section for each OI and full OI guidelines for considerations for ART initiation in the setting of a specific OI.

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MANAGEMENT OF SPECIFIC OIs

NOTE: This resource summarizes guidelines for treatment and prevention of mucocutaneous candidiasis, cryptococcal meningitis, cytomegalovirus (CMV), herpes simplex virus (HSV), disseminated mycobacterium avium complex (MAC), varicella zoster virus (VZV), histoplasmosis, pneumocystis pneumonia (PCP), toxoplasma gondii encephalitis (TE), and cryptosporidiosis. The clinician should refer to the full OI guidelines and prescribing information before prescribing medications for prevention or treatment of OIs.

MUCOCUTANEOUS CANDIDIASIS

Preventing Disease
Routine primary prophylaxis not recommended (AIII)

Special Considerations Regarding ART Initiation
- No evidence to indicate that ART initiation needs to be delayed

Oropharyngeal Candidiasis
Duration of therapy: 7-14 days

Preferred Oral Regimen:
- Fluconazole 100 mg po once daily (AI) **or**

***Preferred Topical Regimens*:**
- Clotrimazole troches 10 mg po 5 times per day (BI) **or**
- Miconazole mucoadhesive buccal tab 50 mg applied once daily (BI) (do not swallow, chew or crush)

Alternative Oral Regimens:
- Itraconazole oral solution 200 mg po once daily (BI) **or**
- Posaconazole oral suspension 400 mg po bid on day 1, then 400 mg po once daily (BI)

Alternative Topical Regimen:
- Nystatin suspension 4-6 mL qid or 1-2 pastilles 4-5 times per day (BII)

Esophageal Candidiasis
Duration of therapy: 14-21 days

NOTE: Systemic antifungals are required for effective treatment (AI). A higher rate of relapse has been reported with echinocandins than with fluconazole.

Preferred Regimens:
- Fluconazole 100-400 mg po or IV once daily (AI) **or**
- Itraconazole oral solution 200 mg po once daily (AI)

Alternative Regimens:
- Voriconazole 200 mg po or IV bid (BI) **or**
- Anidulafungin 100 mg IV for one dose, then 50 mg IV once daily (BI) **or**
- Caspofungin 50 mg IV once daily (BI) **or**
- Micafungin 150 mg IV once daily (BI) **or**
- Amphotericin B deoxycholate 0.6 mg/kg IV once daily (BI) **or**
- Lipid formulation of amphotericin B 3-4 mg/kg IV once daily (BIII)

Azole-refractory oropharyngeal or esophageal candidiasis
- Posaconazole oral suspension 400 mg po bid for 28 days is effective in 75% of pts
- Other options include itraconazole oral solution (effective in 2/3 of pts) (BII), anidulafungin (BII), caspofungin (BII), micafungin (BII), voriconazole (BII)

Uncomplicated Vulvovaginal Candidiasis

Preferred Regimens:
- Fluconazole 150 mg po for 1 dose (AII) **or**
- Topical azole antifungal for 3-7 days (AII)

Alternative Regimen:
- Itraconazole oral solution 200 mg po once daily for 3-7 days (BII)

Severe or Recurrent Vaginitis
- Fluconazole 100-200 mg po once daily **or** topical azole antifungal for ≥ 7 days (AII)

Chronic Suppressive Therapy
- Due to risk of azole resistance, chronic suppressive therapy is usually not recommended unless frequent or severe recurrences (BIII)
- See OI guidelines for additional information

Other Considerations
- Systemic azoles may have significant interactions with ARVs. Please refer to Table 5 of the OI Guidelines and *www.hiv-druginteractions.org* for drug interaction information.

An up-to-date and downloadable PDF file is available online at: ***www.FCAETC.org/treatment***. To order additional printed copies, please email ***orders@fcaetc.org***. If you require an alternate format to accommodate a disability, please email: ***contact@fcaetc.org*** or call ***866.352.2382***.

CRYPTOCOCCAL MENINGITIS

NOTE: See the OI guidelines and Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases 2010; 50: 291-322 (available online at: *http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Cryptococcal.pdf*) for treatment of nonmeningeal cryptococcal infection.

Preventing Disease
Primary prophylaxis or screening for serum cryptococcal antigen in asymptomatic pts is not recommended (BII)

Induction/Consolidation/Maintenance Therapy

Special Considerations Regarding ART Initiation
- Optimal timing of ART initiation is controversial
- Pts with severe cryptococcosis, especially those with ↑ intracranial pressure (ICP) may need to delay ART until after the induction or induction and consolidation phases are completed (i.e., 2-10 weeks). Earlier ART initiation may be needed in pts with advanced immunosuppression (e.g., CD4 count < 50 cells/mm³) (BIII).
- When ART is initiated earlier, monitor for and aggressively address IRIS complications such as ↑ ICP (BIII). See Section on Managing Increased ICP.

Induction Therapy
Duration of Induction Therapy: Treat for ≥ 2 weeks and until CSF culture negative with repeat lumbar puncture (LP), followed by Consolidation Therapy

Preferred Regimen:
- Liposomal amphotericin B 3-4 mg/kg IV once daily + flucytosine 25 mg/kg/dose po qid (AI)

Alternative Regimens:
- Amphotericin B deoxycholate 0.7-1 mg/kg IV once daily + flucytosine 25 mg/kg/dose po qid (AI) **or**
- Amphotericin B lipid complex 5 mg/kg IV once daily + flucytosine 25 mg/kg/dose po qid (BII) **or**
- Liposomal amphotericin B 3-4 mg/kg IV once daily + fluconazole 800 mg po or IV once daily (BIII) **or**
- Amphotericin B deoxycholate 0.7-1 mg/kg IV once daily + fluconazole 800 mg po or IV once daily (BI) **or**
- Liposomal amphotericin B 3-4 mg/kg IV once daily alone (BII) **or**
- Fluconazole 400-800 mg po or IV once daily + flucytosine 25 mg/kg/dose po qid (BII) **or**
- Fluconazole 1200 mg po or IV once daily alone (CII)

Consolidation Therapy
Duration of Consolidation Therapy: Treat for ≥ 8 weeks (AI), followed by Maintenance Therapy

Preferred Regimen:
- Fluconazole 400 mg po or IV once daily (AI)

Alternative Regimen:
- Itraconazole 200 mg po bid (CI)

Chronic Maintenance Therapy

Preferred Regimen:
- Fluconazole 200 mg po once daily for ≥ 1 year (AI)

Stopping Chronic Maintenance Therapy
If the following criteria are fulfilled (BII):
- Completed initial (induction, consolidation) therapy **and**
- ≥ 1 year on maintenance therapy **and**
- Remains asymptomatic from cryptococcal infection **and**
- CD4 count ≥ 100 cells/mm³ and undetectable HIV RNA for ≥ 3 months in response to ART

Restarting Chronic Maintenance Therapy
- CD4 ≤ 100 cells/mm³ (AIII)

CRYPTOCOCCAL MENINGITIS Continued

Treatment Monitoring and Other Considerations
- Amphotericin B formulation toxicities:
  - Monitor pts on amphotericin B products closely for nephrotoxicity and electrolyte disturbances
  - 500-1000 mL normal saline pre-infusion may ↓ nephrotoxicity risk
  - Pre-treatment (30 minutes prior to infusion) with acetaminophen (650 mg), diphenhydramine (25-50 mg), or hydrocortisone (50-100 mg) may be used to ↓ infusion-related adverse effects (BIII)
  - Meperidine (25-50 mg titrated during infusion) may prevent or treat amphotericin B-related rigors (BII)
- Crytropococcal antigen titers in serum or CSF are of no value in monitoring response to therapy and are not recommended
- Flucytosine added to amphotericin B has shown more rapid CSF sterilization, ↓ relapse, and ↑ survival
- Monitor flucytosine blood levels (peak 2 hours after dose = 30-80 mcg/mL) or monitor closely for cytopenias. Dosage should be adjusted in pts with renal insufficiency (BII).
- Consider brief course of glucocorticosteroids for severe symptoms of IRIS (CIII)
- Manage IRIS by continuing antifungal therapy, ART, and reduction of ICP (CIII)
- Infection due to *C. gattii* should be treated similarly to *C. neoformans* (BIII)
- All the triazole antifungals have the potential to interact with certain antiretroviral agents and other anti-infective agents. These interactions are complex and can be bidirectional. See Table 5 of the OI Guidelines and *www.hiv-druginteractions.org* for drug interactions.

Managing Increased ICP
- Opening pressure should always be measured when an LP is performed. Repeated LPs or CSF shunting are essential to effectively manage symptomatic ↑ ICP.
- If ICP persistently ≥ 25 cm H_2O, daily LP (typically remove 20-30 mL of CSF to ↓ opening pressure in half) until symptoms and ICP stable for > 2 days; consider lumbar drain or ventriculostomy if daily LP required (BIII)
- Corticosteroids and mannitol are ineffective in ↓ ICP and are NOT recommended (BII)
- Acetazolamide is considered hazardous therapy for ICP management and is NOT recommended (BII)

CYTOMEGALOVIRUS (CMV)

Preventing Disease
- CMV end-organ disease is best prevented by using ART to maintain CD4 count >100 cells/mm³

CMV Retinitis Acute Treatment
- Systemic therapy can reduce CMV involvement of the contralateral eye and improve pt survival. Acute treatment should be followed by chronic maintenance therapy.

Special Considerations Regarding ART Initiation
- Optimal timing of ART initiation is not clearly defined. Risk of immune reconstitution uveitis ↑ if ART initiated immediately; however, CMV replication should be controlled within 1-2 weeks. Most experts would not delay ART for > 2 weeks for CMV disease, although clinical judgment is needed (CIII).

Sight-Threatening Lesions (Adjacent to the Optic Nerve or Fovea)

Preferred Ocular Regimen:
- Intravitreal injections of ganciclovir (2 mg) **or** foscarnet (2.4 mg) for 1-4 doses over 7-10 days (AIII); **and** one systemic antiviral agent

Preferred Systemic Regimen:
- Valganciclovir 900 mg po bid for 14-21 days, then 900 mg po once daily (AI)

Alternative Systemic Regimens:
- Ganciclovir 5 mg/kg/dose IV q12h for 14-21 days, then 5 mg/kg IV once daily (AI) **or**
- Ganciclovir 5 mg/kg/dose IV q12h for 14-21 days, then valganciclovir 900 mg po once daily (AI) **or**
- Foscarnet 60 mg/kg/dose IV q8h or 90 mg/kg/dose IV q12h for 14-21 days, then 90-120 mg/kg IV once daily (AI) **or**
- Cidofovir 5 mg/kg/per week IV for 2 weeks, then 5 mg/kg every other week. Give saline hydration before and after cidofovir infusion along with probenecid 2 g po 3 hours before and 1 g po 2 hours and 8 hours after the dose (total of 4 g) (BI).
  - Avoid cidofovir if sulfa allergic because of cross hypersensitivity with probenecid

CYTOMEGALOVIRUS (CMV) Continued

For Peripheral Lesions
- Give one preferred or alternative systemic regimen as listed in Sight-Threatening Lesions section (no ocular regimen required)

Immune Recovery Uveitis - the ocular form of IRIS
- Treatment: periocular or oral (short course) corticosteroid (BIII). Some experts add anti-CMV therapy (CIII).

Chronic Maintenance Therapy

NOTE: Select considering lesion size and location, vision in the contralateral eye, pt's immunologic and virologic status and response to ART in consultation with an ophthalmologist

Preferred Regimen:
- Valganciclovir 900 mg po once daily (AI)

Alternative Regimens:
- Ganciclovir 5 mg/kg IV 5-7 times per week (AI) **or**
- Foscarnet 90-120 mg/kg IV once daily (AI) **or**
- Cidofovir 5 mg/kg IV every other week with saline hydration and probenecid as listed in Alternative Systemic Regimens section (BI)

Stopping Chronic Maintenance Therapy
- CMV treatment should continue until CD4 count > 100 cells/mm³ for > 3-6 months in response to ART (AII)
- Consider discontinuation in consultation with an ophthalmologist, considering magnitude and duration of CD4 count ↑, lesion location, contralateral eye vision, and the feasibility of regular (every 3 months) ophthalmologic monitoring (AIII)

Restarting Chronic Maintenance Therapy
- CD4 count < 100 cells/mm³ (AIII)

CMV Esophagitis or Colitis
Duration of Therapy: 21-42 days or until symptoms resolved (CII), maintenance therapy not indicated unless relapses occur (BII)

Preferred Regimen:
- Ganciclovir 5 mg/kg/dose IV q12h, may switch to valganciclovir 900 mg po q12h when pt can tolerate po therapy (BI)

Alternative Regimens:
- Foscarnet 60 mg/kg/dose IV q8h or 90 mg/kg/dose IV q12h (BI) for pts with treatment limiting toxicity to ganciclovir or with ganciclovir resistance **or**
- Valganciclovir 900 mg po q12h if symptoms not severe enough to interfere with absorption (BII)
- For mild cases: If ART can be initiated or optimized without delay, consider withholding CMV therapy (CIII)

Histologically Confirmed CMV Pneumonitis
- IV ganciclovir or IV foscarnet dosed as in CMV retinitis (CIII)
- Role of oral valganciclovir and optimal duration not established
- Duration of therapy not established

CMV Neurological Disease
- Prompt initiation of ganciclovir 5 mg/kg/dose IV q12h + (foscarnet 90 mg/kg/dose IV q12h or 60 mg/kg/dose IV q8h) until neurologic symptoms resoved (CIII)
- Optimize ART to achieve viral suppression and immune reconstitution (BIII)

HERPES SIMPLEX VIRUS (HSV)

Preventing Disease
Use of antivirals to prevent primary infection is not recommended (BIII)

HSV Treatment

Special Considerations Regarding ART Initiation
- Presence of orolabial HSV should not influence decision of when to start ART. Most pts who have immune reconstitution in response to ART have improvements in frequency or severity of genital HSV episodes. Orolabial HSV that is refractory to therapy or disseminated HSV should warrant more rapid ART initiation (CIII).

Treating Orolabial Lesions (AIII) or Initial or Recurrent Genital Lesions (AI)
Duration of Therapy: 5-10 days for orolabial; 5-14 days for genital
- Valacyclovir 1 g po bid **or**
- Famciclovir 500 mg po bid **or**
- Acyclovir 400 mg po tid

HERPES SIMPLEX VIRUS (HSV) Continued

Treating Severe Mucocutaneous HSV Infections
- Initial therapy: acyclovir 5 mg/kg/dose IV q8h (AIII)
- After lesions begin to regress, change to oral therapy as above; treat until healed

Chronic Suppressive Therapy - for severe or to ↓ frequency of recurrences (AI)
Treat continuously without regard to CD4 count improvement:
- Valacyclovir 500 mg po bid **or**
- Famciclovir 500 mg po bid **or**
- Acyclovir 400 mg po bid

Acyclovir-Resistant Mucocutaneous HSV infections

Preferred Regimen:
- Foscarnet 80-120 mg/kg/day IV in 2-3 divided doses until clinical response (AI)

Alternative Regimens:
Duration of Therapy: 21-28 days or longer, based on clinical response (CIII)
- Topical trifluridine **or**
- Topical cidofovir **or**
- Topical imiquimod **or**
- IV cidofovir (dose as in CMV retinitis)

NOTE: Topical formulations of trifluridine and cidofovir are not commercially available but can be compounded

DISSEMINATED MYCOBACTERIUM AVIUM COMPLEX (MAC)

Preventing 1st Episode of Disseminated MAC Disease (Primary Prophylaxis)
- See beginning section of this resource for indications for primary prophylaxis, recommended regimens, and criteria for stopping primary prophylaxis

Disseminated MAC Disease Treatment
Special Considerations Regarding ART Initiation
- Start ART within 2 weeks after initiating anti-MAC treatment in those not previously treated or not receiving effective ART (CIII)
- If ART already started, continue and optimize unless drug interactions prevent safe concomitant use of ART and anti-MAC medications (CIII)

Preferred Regimens:
At least 2 drugs as initial therapy to prevent or delay emergence of resistance (AI)
- Clarithromycin 500 mg po bid + ethambutol 15 mg/kg po once daily (AI) **or**
- Azithromycin 500-600 mg po once daily + ethambutol 15 mg/kg po once daily (AII) when clarithromycin cannot be used due to drug interactions or intolerance

NOTE: Testing of susceptibility to clarithromycin or azithromycin is recommended

Alternative Regimens:
Consider third or fourth drug if CD4 count < 50 cells/mm³, mycobacterial load > 2 log Colony Forming Units (CFU)/mL blood, or in the absence of effective ART (CIII)
The 3rd or 4th drug options may include:
- Rifabutin 300 mg po once daily (CI) (adjusted dosage may be necessary) **or**
- An aminoglycoside (CIII) such as amikacin 10-15 mg/kg IV once daily **or** streptomycin 1 g IV or IM once daily **or**
- A fluoroquinolone (CIII) such as levofloxacin 500 mg po once daily **or** moxifloxacin 400 mg po once daily

Chronic Maintenance Therapy (Secondary Prophylaxis)
- Same as treatment regimens

Criteria for Stopping Chronic Maintenance Therapy (AII)
- Completed ≥ 12 months therapy and no signs/symptoms MAC **and**
- CD4 count > 100 cells/mm³ for > 6 months in response to ART

Indication for Restarting Secondary Prophylaxis
- CD4 count < 100 cells/mm³ (AIII)

Other Considerations
- NSAIDs may be used for pts who experience moderate to severe symptoms attributed to IRIS (CIII)
- If IRIS symptoms persist, a short term course (4-8 weeks) of systemic corticosteroid (equivalent to 20- 40 mg of prednisone) can be used (CII)

VARICELLA ZOSTER VIRUS (VZV)

Pre-Exposure Prevention of VZV Primary Infection

Indications

- Pts with CD4 count ≥ 200 cells/mm³ without prior vaccination, healthcare provider diagnosis or verification of varicella or herpes zoster history, laboratory confirmation of disease, or known seronegative for VZV (CIII)

NOTE: Routine VZV serologic testing in HIV-infected adults and adolescents is not recommended

Vaccination

- Primary varicella vaccination (Varivax®) 0.5 mL SQ for 2 doses, given ≥ 3 months apart (CIII)
- If vaccination results in disease (rare), treat with acyclovir (AIII)
- VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated (BIII)
- If post-exposure varicella-zoster immune globulin (Varizig®) has been given, wait ≥ 5 months to give VZV vaccination (CIII)
- If post-exposure acyclovir or valacyclovir has been given, wait ≥ 3 days after last antiviral dose to give VZV vaccination (CIII)

Post-Exposure Prophylaxis

NOTE: Studies lacking in HIV-infected adults/adolescents

Indication

Close contact with a person who has active varicella or herpes zoster, and is susceptible to VZV (i.e., has no history of vaccination or of either condition, or is known to be VZV seronegative) (AIII)

Preferred Post-Exposure Prophylaxis:

- Varizig® 125 International Units per 10 kg (maximum of 625 International Units) IM, given as soon as possible and within 10 days after exposure to a person with active varicella or herpes zoster (AIII)
- Varizig® can only be obtained by contacting FFF Enterprises at: 800.843.7477

Alternative Prophylaxis (Beginning 7-10 days post exposure):

- Acyclovir 800 mg po 5 times per day for 5-7 days (BIII) **or**
- Valacyclovir 1 g po tid for 5-7 days (BIII)

Treatment of Varicella Infections

Special Considerations Regarding ART Initiation

- A single episode of zoster is not an indication to initiate or defer ART. Strongly consider ART initiation in pts who have multiple recurrences of zoster or complications from VZV disease (e.g., encephalitis) (AIII). Immune reconstitution is associated with an ↑ risk of VZV reactivation.

Primary Varicella Infection (Chickenpox) - Uncomplicated Cases

Duration of Therapy: 5-7 days

Preferred Regimens:

- Valacyclovir 1 g po tid (AII) **or**
- Famciclovir 500 mg po tid (AII)

Alternative Regimen:

- Acyclovir 800 mg po 5 times per day (BII)

Primary Varicella Infection (Chickenpox) - Severe or Complicated Cases

Duration of Therapy: 7-10 days

Acyclovir 10-15 mg/kg/dose IV q8h (AIII)

- May switch to oral famciclovir, valacyclovir, or acyclovir if defervescence and no visceral involvement evident (BIII)

Herpes Zoster - Acute Localized Dermatomal (Shingles)

Duration of Therapy: 7-10 days or longer if lesions resolve slowly

Preferred Regimens:

- Valacyclovir 1 g po tid (AII) **or**
- Famciclovir 500 mg po tid (AII)

Alternative Regimen:

- Acyclovir 800 mg po 5 times per day (BII)

Herpes Zoster - Extensive Cutaneous or Visceral Involvement

- Acyclovir 10-15 mg/kg/dose IV q8h until clinical improvement is evident (AII)
- Switch to oral therapy (valacyclovir 1 g po tid, or famciclovir 500 mg po tid, or acyclovir 800 mg po 5 times per day) - to complete a 10-14 day course, when new lesions have ceased and signs and symptoms of visceral VZV infection improving (BIII)

Progressive Outer Retinal Necrosis

- Involvement of experienced ophthalmologist strongly recommended (AIII)
- (Ganciclovir 5 mg/kg/dose and/or foscarnet 90 mg/kg/dose) IV q12h + (ganciclovir 2 mg/0.05 mL and/or foscarnet 1.2 mg/0.05 mL) intravitreal twice weekly (AIII)
- Optimize ART regimen (AIII)
- Treatment duration not well defined - base on clinical, virologic, and immunologic responses in consultation with ophthalmologist

Acute Retinal Necrosis

- Acyclovir 10-15 mg/kg/dose IV q8h for 10-14 days, followed by valacyclovir 1 g po tid for 6 weeks + ganciclovir 2 mg/0.05 mL intravitreal twice weekly for 1-2 doses (AIII)
- Many experts would include ganciclovir 2 mg/0.05 mL intravitreal twice weekly for 1-2 doses with initial regimen (BIII)
- Involvement of an experienced ophthalmologist is strongly recommended (AIII)
- Treatment duration not well defined - base on clinical, virologic, and immunologic responses in consultation with ophthalmologist

HISTOPLASMOSIS *(Histoplasma capsulatum)*

Preventing 1st Episode of *Histoplasma capsulatum* Infection (Primary Prophylaxis)

Indications for Primary Prophylaxis

- CD4 count < 150 cells/mm³ and high risk of occupational exposure or living in a community with > 10 cases/100 pt-years (BI)

Preferred Regimen:

- Itraconazole 200 mg po once daily (BI)

Stopping Primary Prophylaxis

- CD4 count ≥ 150 cells/mm³ for ≥ 6 months on ART (BIII)

Indication for Restarting Primary Prophylaxis

- CD4 count < 150 cells/mm³ (BIII)

Histoplasmosis Treatment

Special Considerations Regarding ART Initiation

- Start ART as soon as possible after initiating antifungal therapy (AIII)
- IRIS is uncommon with histoplasmosis
- Drug interactions may be complex. See Table 5 of OI Guidelines or *www.hiv-druginteractions.org* for drug interactions.

Moderately Severe to Severe Disseminated Disease

Induction Therapy

Duration of Therapy: ≥ 2 weeks or until clinically improved followed by maintenance therapy

Preferred Regimen:

- Liposomal amphotericin B 3 mg/kg IV once daily (AI)

Alternative Regimen:

- Amphotericin B lipid complex (ABLC) **or** amphotericin B cholesteryl sulfate complex (ABCD) 3 mg/kg IV once daily (AIII)

Maintenance Therapy

Duration of Maintenance Therapy: ≥ 12 months

Preferred Regimen:

- Itraconazole 200 mg po tid for 3 days, then 200 mg po bid (AII), with dosage adjustment based on interactions with ARV and itraconazole serum concentration

Less Severe Disseminated Disease

Induction and Maintenance Therapy

Duration of Therapy: ≥ 12 months

Preferred Regimen:

- Itraconazole 200 mg po tid for 3 days, then 200 mg po bid (AII), with dosage adjustment based on interactions with ARV and itraconazole serum concentration

Alternative Regimens:

NOTE: These recommendations are based on limited clinical data (for pts intolerant to itraconazole who are only moderately ill)

- Posaconazole 400 mg po bid (BIII) **or**
- Voriconazole 400 mg po bid for 1 day, then 200 mg po bid (BIII) **or**
- Fluconazole 800 mg po once daily (CII)

HISTOPLASMOSIS Continued

Histoplasma Meningitis

Induction Therapy

Duration of Therapy: 4–6 Weeks followed by maintenance therapy

- Liposomal amphotericin B 5 mg/kg IV once daily (AIII)

Maintenance Therapy

- Itraconazole 200 mg po bid - tid for ≥ 12 months and until resolution of abnormal CSF findings with dosage adjustment based on interactions with ARV and itraconazole serum concentration (AIII)

Long-Term Suppressive Therapy (Secondary Prophylaxis)

Indications

- For pts with severe disseminated or CNS infection after completion of ≥ 12 months of treatment (AIII) **and**
- In pts who relapsed despite appropriate initial therapy (BIII)

Preferred Regimen:

- Itraconazole 200 mg po once daily (AIII)

Alternative Regimen:

- Fluconazole 400 mg po once daily (BIII)

Criteria for Stopping Long Term Suppressive Therapy (AI)

- Received azole treatment for > 1 year **and**
- Negative fungal blood cultures **and**
- Serum Histoplasma antigen < 2 ng/mL **and**
- CD4 count > 150 cells/mm³ for ≥ 6 months in response to ART

Indication for Restarting Secondary Prophylaxis

- CD4 count < 150 cells/mm³ (BIII)

Other Considerations

- Itraconazole Theraputic Drug Monitoring (TDM) recommended (AIII). Random serum (itraconazole + hydroxyitraconazole) target > 1 mcg/mL after 2 weeks of therapy.
- Itraconazole oral solution preferred over capsule (improved absorption, but less well tolerated); however, this formulation may not be necessary if itraconazole concentration is increased by concomitant use of a CYP3A4 inhibitor such as ritonavir-boosted PIs
- Acute pulmonary histoplasmosis in HIV-infected pts with CD4 count > 300 cells/mm³ should be managed the same as for non-immunocompromised pts (AIII)
- All the triazole antifungals have the potential to interact with certain ARVs and other anti-infective agents. These interactions are complex and can be bidirectional. See Table 5 of OI Guidelines or *www.hiv-druginteractions.org* for drug interactions.

PNEUMOCYSTIS PNEUMONIA (PCP)

Preventing 1st Episode of PCP (Primary Prophylaxis)

- See beginning section of this resource for indications for primary prophylaxis, recommended regimens, and criteria for stopping primary prophylaxis

PCP Treatment

Special Considerations Regarding ART Initiation

- If not on ART, initiate within 2 weeks of PCP diagnosis, when possible (AI) IRIS has been reported following PCP. Symptoms include fever and recurrence or exacerbation of pulmonary symptoms; however, it has only rarely been life-threatening. Management is not well-defined. Some experts would consider corticosteroid if other causes of respiratory therapy are ruled out.

NOTE: Pts who develop PCP despite TMP-SMX prophylaxis usually can be treated effectively with standard doses of TMP-SMX (BIII). Adjunctive corticosteroid may be indicated in some moderate to severe cases (see indications and dosage recommendations below).

Moderate to Severe PCP

Duration of Therapy: 21 days based on clinical improvement (AII) followed by secondary prophylaxis

Preferred Regimen:

- TMP-SMX: (TMP 15-20 mg/kg/day and SMX 75-100 mg/kg/day) IV given q6h or q8h (AI), may switch to po after clinical improvement (AI)

Alternative Regimens:

- Pentamidine 4 mg/kg IV once daily over ≥ 60 minutes (AI); may ↓ to 3 mg/kg IV once daily if toxicities (BI) **or**
- Primaquine[7] 30 mg (base) po once daily + clindamycin (600 mg IV q6h or 900 mg IV q8h) or (450 mg po q6h or 600 mg po q8h) (AI)

Adjunctive Corticosteroids:

For Moderate to Severe PCP (PaO_2 < 70 mmHg at room air **or** Alveolar-arterial O_2 gradient ≥ 35 mmHg) (AI)

Dosing Schedule:

- Prednisone doses (beginning as early as possible and within 72 hours of PCP therapy) (AI):
  - Days 1-5, 40 mg po bid
  - Days 6-10, 40 mg po once daily
  - Days 11-21, 20 mg po once daily
- IV methylprednisolone can be given as 75% of prednisone dose

Mild to Moderate PCP

Duration of Therapy: 21 days based on clinical improvement (AII) followed by secondary prophylaxis

Preferred Regimens:

- TMP-SMX: (TMP 15-20 mg/kg/day and SMX 75-100 mg/kg/day), given po in 3 divided doses (AI) **or**
- TMP-SMX 2 DS po tid (AI)

Alternative Regimens:

- Dapsone[7] 100 mg po once daily + TMP 15 mg/kg/day po divided tid (BI) **or**
- Primaquine[7] 30 mg (base) po once daily + clindamycin 450 mg po q6h or 600 mg po q8h (BI) **or**
- Atovaquone 750 mg po bid (BI)

Preventing Subsequent Episode of PCP (Secondary Prophylaxis)

Preferred Regimens:

- TMP-SMX 1 DS po once daily[8] (AI) **or**
- TMP-SMX 1 SS po once daily[8] (AI)

Alternative Regimens:

- TMP-SMX 1 DS po 3 times per week[8] (BI) **or**
- Dapsone[7,9]100 mg po once daily or 50 mg po bid (BI) **or**
- Dapsone[7] 50 mg po once daily + (pyrimethamine 50 mg + leucovorin 25 mg) po once weekly (BI) **or**
- (Dapsone[7] 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) po once weekly (BI) **or**
- Aerosolized pentamidine[9] 300 mg via Respirgard II® nebulizer every month (BI) **or**
- Atovaquone 1500 mg po once daily (BI) **or**
- (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) po once daily (CIII)

Indications for Stopping Secondary Prophylaxis

- CD4 count ↑ from < 200 cells/mm³ to > 200 cells/mm³ for > 3 months as a result of ART (BII) **or**
- If PCP diagnosed at CD4 count > 200 cells/mm³, prophylaxis should probably be lifelong regardless of CD4 count rise as a consequence of ART (BIII)

Indication for Restarting Secondary Prophylaxis

- CD4 count falls to < 200 cells/mm³ (AIII)

Other Considerations

- If non-life-threatening adverse reactions to TMP-SMX, continue the drug if clinically feasible
- If TMP-SMX is discontinued for mild adverse reaction, re-institution should be considered after the reaction has resolved (AII). The dose can be increased gradually (desensitization) (BI) or given at a reduced dose or frequency (CIII).
- Therapy should be permanently discontinued, with no rechallenge, in pts with possible or definite Stevens-Johnson Syndrome or toxic epidermal necrolysis (AIII)

7. Whenever possible, pts should be tested for G6PD deficiency before giving dapsone or primaquine. Alternative agent should be used if the pt is found to have G6PD deficiency.
8. TMP-SMX DS once daily also confers protection against toxoplasmosis and many respiratory bacterial infections; lower dose also likely confers protection.
9. Aerosolized pentamidine or dapsone (without pyrimethamine) should not be used for PCP prophylaxis in pts who are seropositive for *Toxoplasma gondii*.

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TOXOPLASMA GONDII ENCEPHALITIS (TE)

Preventing 1st Episode of Toxoplasmosis (Primary Prophylaxis)

- See beginning section of this resource for indications for primary prophylaxis, recommended regimens, and criteria for stopping primary prophylaxis

Treatment of Acute TE Infection

Special Considerations Regarding ART Initiation

- Start ART within 2-3 weeks of TE diagnosis (CIII)

Total Duration for Treating Acute TE Infection: ≥ 6 weeks (BII); longer if clinical or radiologic disease is extensive or if response incomplete at 6 weeks. Follow acute treatment with chronic maintenance therapy.

Preferred Regimen (AI):

- Pyrimethamine 200 mg po once, followed by dose based on weight:
  - Weight ≤ 60 kg: pyrimethamine 50 mg po once daily + sulfadiazine 1000 mg po q6h + leucovorin 10-25 mg po once daily (can ↑ to 50 mg po once daily or bid)
  - Weight > 60 kg: pyrimethamine 75 mg po once daily + sulfadiazine 1500 mg po q6h + leucovorin 10-25 mg po once daily (can ↑ to 50 mg po once daily or bid)

Alternative Regimens:

- (Pyrimethamine + leucovorin)[10] + clindamycin 600 mg IV or po q6h (AI); preferred alternative if intolerant of sulfadiazine or if did not respond to pyrimethamine-sulfadiazine; must add additional agent for PCP prophylaxis **or**
- TMP-SMX (TMP 5 mg/kg/dose and SMX 25 mg/kg/dose) IV or po bid (BI) **or**
- Atovaquone 1500 mg po bid + (pyrimethamine + leucovorin)[10] (BII) **or**
- Atovaquone 1500 mg po bid + sulfadiazine[11] (BII) **or**
- Atovaquone 1500 mg po bid (BII) **or**
- (Pyrimethamine + leucovorin)[10] + azithromycin 900-1200 mg po once daily (CII)

Chronic Maintenance Therapy

Preferred Regimen:

- Pyrimethamine 25-50 mg po once daily + sulfadiazine 2000-4000 mg po per day (in 2 to 4 divided doses) + leucovorin 10-25 mg po once daily (AI)

Alternative Regimens:

- Clindamycin 600 mg po q8h + (pyrimethamine 25-50 mg + leucovorin 10-25 mg) po once daily (BI); must add additional agent to prevent PCP (AII) **or**
- TMP-SMX 1 DS po bid (BII) **or**
- Atovaquone 750-1500 mg po bid + (pyrimethamine 25 mg + leucovorin 10 mg) po once daily (BII) **or**
- Atovaquone 750-1500 mg po bid + sulfadiazine 2000-4000 mg po per day (in 2 to 4 divided doses) (BII) **or**
- Atovaquone 750-1500 mg po bid (BII)

TOXOPLASMA GONDII ENCEPHALITIS Continued

Criteria for Stopping Chronic Maintenance Therapy

- Successfully completed initial therapy, no signs or symptoms of TE, and CD4 count > 200 cells/mm³ for > 6 months in response to ART (BI)

Criteria for Restarting Chronic Maintenance Therapy

- CD4 count < 200 cells/mm³ (AIII)

Other Considerations

- Give adjunctive corticosteroids (e.g., dexamethasone) only when clinically indicated to treat mass effect associated with focal lesions or associated edema (BIII); discontinue as soon as clinically feasible
- Anticonvulsants should be given to pts with a history of seizures (AIII) and continued at least through the period of acute treatment; anticonvulsants **should not be used** as seizure prophylaxis (BIII)

10. Pyrimethamine and leucovorin dosed as in Preferred Regimen for Acute Infection.
11. Sulfadiazine weight-based dose as in Preferred Regimen for Acute Infection.

CRYPTOSPORIDIOSIS

Preventing Disease

Initiation of ART before the pt becomes severely immunocompromised should prevent disease (AII)

Preferred Management Strategy:

- Initiate or optimize ART to achieve CD4 count > 100 cells/mm³ (AII)

Alternative Management Strategies:

- Optimize ART **and**
- Nitazoxanide 500-1000 mg po bid for 14 days (CIII) **or**
- Paromomycin 500 mg po qid for 14-21 days (CIII)

NOTE: All treatment includes adequate fluid/electrolyte replacement and anti-motility agents as needed (AIII). Diarrhea can cause lactase deficiency, pts should avoid milk products (CIII).

HEPATITIS

See F/C AETC Hepatitis in HIV/AIDS Treatment Guideline Resource at: *www.fcaetc.org/treatment/hepatitis.pdf*

MYCOBACTERIUM TUBERCULOSIS

See F/C AETC Treatment of Tuberculosis in HIV/AIDS, Treatment Guideline Resource at: *www.fcaetc.org/treatment/tb.pdf*

Dosage Forms and Food Restrictions for Drugs Used to Prevent or Treat OIs

NOTE: The clinician should refer to the full OI guidelines, prescribing information and other resources to review important information such as precautions, adverse effects and drug interactions before prescribing medications for prevention or treatment of OIs. This is not a comprehensive list of available dosage forms.

Adverse Effects: See *Table 6 page U-47* of the OI Guidelines for common or serious adverse reactions for drugs used for OIs
Drug Interactions: See *Table 5 page U-33* of the OI Guidelines or *www.hiv-druginteractions.org* for significant drug interactions

Drug	Dosage Forms	Food Restrictions	Hepatic/Renal Alerts
Acyclovir (Zovirax®)	200 mg cap, 400, 800 mg tab 💧 🔑	⊘ ⊗	R
Amikacin	Injection (250, 500, 1000 mg) vial		R
Amphotericin B cholesteryl sulfate complex (Amphotec®)	Injection (50, 100 mg) vial		R
Amphotericin B deoxycholate (Fungizone®)	Injection (50 mg) vial		R
Amphotericin B lipid complex (Abelcet®)	Injection (100 mg) vial		R
Amphotericin B liposomal (AmBisome®)	Injection (50 mg) vial		R
Anidulafungin (Eraxis®)	Injection (50, 100 mg) vial		H
Atovaquone (Mepron®)	750 mg/5mL oral susp (5 mL packet, 210 mL bottle)	⊘	H
Azithromycin (Zithromax®)[12]	250, 500, 600 mg tab 💧 🔑	⊘ ⊗	H R
Caspofungin (Cancidas®)	Injection (50, 70 mg) vial		H
Cidofovir (Vistide®)	Injection (75, 375 mg) vial		R
Clarithromycin (Biaxin®)	250, 500 mg tab, 500 mg XL (extended release) tab 💧	⊘ ⊗ / XL ⊘	H R
Clindamycin (Cleocin®)	75, 150, 300 mg cap 💧	⊘ ⊗	H
Clotrimazole (Mycelex®)	10 mg troche	⊗	H
Dapsone	25, 100 mg tab	⊘ ⊗	H
Ethambutol (Myambutol®)[13]	100, 400 mg tab	⊘	H R
Famciclovir (Famvir®)	125, 250, 500 mg tab	⊘ ⊗	R
Fluconazole (Diflucan®)	50, 100, 150, 200 mg tab 💧 🔑	⊘ ⊗	H R
Flucytosine (Ancobon®)	250, 500 mg cap	⊘ ⊗	H R
Foscarnet (Foscavir®)	Injection (600, 1200 mg) vial		R
Ganciclovir (Cytovene®)	Injection (500 mg) vial		R
Itraconazole (Sporanox®)[14,15]	100 mg cap, 200 mg tab,100 mg/10 mL oral soln 🔑	caps, tab ⊘ / 💧 ⊗	H
Levofoxacin (Levaquin®)[16]	250, 500, 750 mg tab 💧 🔑	⊘ ⊗	H R
Leucovorin calcium (Folinic acid)	5, 10, 15, 25 mg tab 🔑	⊘ ⊗	
Micafungin (Mycamine®)	Injection (50, 100 mg) vial		H R
Moxifloxacin (Avelox®)[17]	400 mg tab 🔑	⊘ ⊗	H R
Nitazoxanide (Alinia®)	500 mg tab, 100 mg/5 mL oral susp	⊘	
Nystatin (Mycostatin®)	100,000 units/mL oral susp	⊗	
Paromomycin	250 mg cap	⊘	R
Pentamidine (NebuPent®, Pentam®)	Inhalation (300 mg) vial, Injection (300 mg) vial		H R
Posaconazole (Noxafil®)[18]	200 mg/5 mL oral susp 🔑	⊘	H R
Primaquine	26.3 mg (15 mg base) tab	⊘	H
Probenecid	500 mg tab	⊘	R
Pyrimethamine (Daraprim®)	25 mg tab	⊘	H
Rifabutin (Mycobutin®)	150 mg cap	⊘	R
Streptomycin	Injection (1 g) vial		R
Sulfadiazine	500 mg tab	⊘ ⊗	H R
Trimethoprim/sulfamethoxazole (TMP-SMX) (Septra®, Bactrim®)	TMP-SMX component: 160 mg/800 mg (DS tab), 80 mg/400 mg (SS tab) 💧 🔑	⊘ ⊗	H R
Valacyclovir (Valtrex®)	500, 1000 mg cap	⊘ ⊗	R
Valganciclovir (Valcyte®)[19]	450 mg tab	⊘	R
Voriconazole (Vfend®)[20]	50, 200 mg tab 💧 🔑	⊗	H R

💧 = Liquid available 🔑 = Injection available ⊘ = Give with food ⊗ = Give without food ⊘ ⊗ = Give with/without food

H = Requires hepatic dosage adjustment and/or has precaution for use in hepatic impairment. R = Requires renal dosage adjustment and/or has precaution for use in renal insufficiency (See the OI Guidelines and product package inserts for information about renal or hepatic dosing, adverse effects, and precautions.)

12. Give azithromycin 1 hour before or 2 hours after giving aluminum/magnesium-containing antacids.
13. Separate ethambutol by 4 hours from aluminum-containing antacids.
14. Itraconazole soln generally preferred due to ↑ bioavailability but not tolerated as well. May not be necessary when itraconazole TDM performed.
15. Acid reducing agents ↓ itraconazole absorption. Give antacids ≥ 1 hour before or 2 hours after itraconazole. Give with cola beverage if used with other acid reducing agents.
16. Give 2 hours before or after any medication containing divalent or trivalent cations (e.g., calcium carbonate, iron).
17. Give 4 hours before or 8 hours after iron, magnesium, aluminum, or zinc containing vitamins or medications.
18. Give posaconazole with a full meal (high fat preferred) or nutritional supplement. Give with an acidic carbonated drink (e.g., cola) if unable to eat a full meal or nutritional supplement. A tab formulation is available but is only indicated for prevention of invasive fungal infections in severely immunocompromised pts.
19. Do not crush or break tabs. An oral solution is available but is indicated only for prevention of CMV in pediatric pts.
20. Give voriconazole tabs or susp ≥ 1 hour before or after meals.