Toxoplasmosis (Last updated October 29, 2015; last reviewed October 29, 2015)

Panel's Recommendations

Preventing Exposure

- Ingestion of undercooked meats that could contain tissue cysts and contact with cat feces that could contain sporulated oocysts should be avoided **(AIII)**.

Initiating Primary Prophylaxis

- *Toxoplasma*-seropositive children aged <6 years with CD4 T lymphocyte (CD4) cell percentage <15% and children aged ≥6 years with CD4 <100 cells/mm^3 should be administered prophylaxis against *Toxoplasma* encephalitis (TE) **(AIII)**. The preferred agent for prophylaxis of TE is trimethoprim-sulfamethoxazole, one double-strength tablet daily for adolescents and adults (or weight-equivalent dosing for children) **(AII*)**.
- Primary preventive therapy can be discontinued once a child responds to combination antiretroviral therapy (cART) with a sustained rise in CD4 percentage above 15% for children <6 years of age, and >200 cells/mm^3 for children aged ≥6 years **(BIII)**
- Most experts recommend treating pregnant women with acute toxoplasmosis in an attempt to prevent fetal infection **(BII)**. For more extensive information on diagnosis, prevention, and treatment of pregnant women with toxoplasmosis, please see the *Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*.
- Empiric therapy should be strongly considered for newborns of HIV-infected mothers who had symptomatic or asymptomatic primary Toxoplasma infection during pregnancy, regardless of whether treatment was administered during pregnancy **(BIII)**.
- The preferred treatment for congenital toxoplasmosis is pyrimethamine combined with sulfadiazine, with supplementary leucovorin **(AII)**.
- The recommended duration of treatment of congenital toxoplasmosis in HIV-infected infants is 12 months **(AIII)**.
- Therapy for acquired toxoplasmosis in HIV-infected children is sulfadiazine plus pyrimethamine and leucovorin **(AI*)**. Please refer to http://www.daraprimdirect.com for information regarding access to pyrimethamine. If pyrimethamine is unavailable clinicians may substitute trimethoprim-sulfamethoxazole, dosed according to age and weight, in place of the combination of sulfadiazine, pyrimethamine, and leucovorin.
- Corticosteroids are recommended for HIV-infected children with central nervous system toxoplasmosis when cerebrospinal fluid protein is highly elevated (i.e., >1,000 mg/dL) or who have focal lesions with substantial mass effect **(BIII)**. Anticonvulsants should be administered only to children with TE who have a history of or current seizures **(AIII)**.
- Complete blood count should be monitored weekly in patients taking daily pyrimethamine **(AIII)**. Patients who have completed initial therapy for TE should be given suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) unless cART results in immune reconstitution **(AI*)**.
- The preferred regimen for suppressive therapy for TE is sulfadiazine plus pyrimethamine and leucovorin **(AI*)**. Please refer to http://www.daraprimdirect.com for information regarding access to pyrimethamine. If pyrimethamine is unavailable clinicians may substitute trimethoprim-sulfamethoxazole dosed according to age and weight.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Epidemiology

The major mode of transmission of *Toxoplasma gondii* infection to infants and young children is congenital, occurring almost exclusively in neonates born to women who sustain primary *Toxoplasma* infection during pregnancy. The estimated incidence of congenital toxoplasmosis in the United States is one case per 1,000 to 12,000 live-born infants.[1,2] The seroprevalence of *T. gondii* in U.S.-born individuals aged 12 to 49 years declined from 14.1% in the National Health and Nutrition Examination Survey from 1988 to 1994 to 9.0% from 1999 to 2004.[3] Older children, adolescents, and adults typically acquire *Toxoplasma* infection by eating undercooked meat that contains parasitic cysts or by unintentionally ingesting sporulated oocysts from cat

feces in soil or contaminated food or water.[4] In the United States, eating raw shellfish including oysters, clams, and mussels was recently identified as a novel risk factor for acute infection.[5] Cats are the only definitive host for *T. gondii*. However, cats excrete oocysts in their feces only transiently after initial infection, and most studies have failed to show a correlation between cat ownership and *Toxoplasma* infection in humans. Indeed, *Toxoplasma* infection in humans in the United States has declined despite increased cat ownership.[4]

The overall risk of maternal-fetal transmission in HIV-uninfected women who acquire primary *Toxoplasma* infection during pregnancy is 29% (95% confidence interval [CI], 25%–33%), with variation depending upon the trimester during which primary maternal infection occurs.[6] The risk of congenital infection is low among infants born to women who become infected during the first trimester (range: 2%–6%) but increases sharply thereafter, with a risk as high as 81% in women who become infected during the last few weeks of pregnancy.[6,7] Infection of the fetus in early gestation usually results in more severe disease than does infection late in gestation.

The prevalence of latent *Toxoplasma* infection in HIV-infected and HIV–uninfected women in the United States was assessed in a cross-sectional study of 2,525 non-pregnant women enrolled in the Women's Interagency Health Study.[8] The prevalence of *Toxoplasma* seropositivity was 15% and did not differ by HIV infection status. The overall rate of mother-to-child transmission (MTCT) of *Toxoplasma* in HIV-infected pregnant women is unknown; however, a few cases of MTCT of *Toxoplasma* in HIV-infected women have been reported.[9-13] HIV-infected women may be at increased risk of transmitting *T. gondii* to their fetuses, and serologic testing for *Toxoplasma* should be performed on all HIV-infected pregnant women. Prenatal transmission of *T. gondii* is rare from women without HIV infection who acquired chronic *Toxoplasma* infection before pregnancy.[14] However, with HIV coinfection, perinatal transmission of *Toxoplasma* has been observed in women with chronic *Toxoplasma* infection (transmission rate: <4%), presumably because of reactivation of replication of the organism in women who are severely immunosuppressed.[9-12]

Central nervous system (CNS) infection with *T. gondii* was reported as an AIDS-indicator condition in <1% of pediatric AIDS cases before the advent of combination antiretroviral therapy (cART).[15] Since then, this condition is rarely encountered in HIV-infected U.S. children. CNS toxoplasmosis occurred in 5 of 2,767 (0.2%) HIV-infected children enrolled in the long-term follow-up study Pediatric AIDS Clinical Trials Group 219c since cART has been available.[16] Infection is considered to have occurred *in utero* in most cases of *Toxoplasma* encephalitis (TE) seen in HIV-infected children.

More rarely, it has been reported in older HIV-infected children, who presumably had primary acquired toxoplasmosis.[17-19] As in adults, the greatest risk is among severely immunosuppressed children (i.e., CD4 T lymphocyte [CD4] cell count <50 cells/mm^3).

Clinical Manifestations

In studies of non-immunocompromised infants with congenital toxoplasmosis, most infants (70%–90%) are asymptomatic at birth. However, most asymptomatic children develop late sequelae (i.e., retinitis, visual impairment, and intellectual or neurologic impairment), with onset of symptoms ranging from several months to years after birth. Symptoms in newborns take either of two presentations: generalized disease or predominantly neurologic disease. Symptoms can include maculopapular rash; generalized lymphadenopathy; hepatosplenomegaly; jaundice; hematologic abnormalities including anemia, thrombocytopenia, and neutropenia; and substantial CNS disease including hydrocephalus, intracerebral calcification, microcephaly, chorioretinitis, and seizures.[20]

Toxoplasmosis acquired after birth most often is initially asymptomatic. When symptoms occur, they are frequently nonspecific and can include malaise, fever, sore throat, myalgia, lymphadenopathy (cervical), and a mononucleosis-like syndrome featuring a maculopapular rash and hepatosplenomegaly.[21]

TE should be considered in all HIV-infected children with new neurologic findings, but especially those with severe immunosuppression. Although focal findings are typical, the initial presentation can vary and reflect

diffuse CNS disease. Generalized symptoms include fever, reduced alertness, and seizures.

Isolated ocular toxoplasmosis is rare in immunocompromised children and usually occurs in association with CNS infection. As a result, a neurologic examination is indicated for children in whom *Toxoplasma* chorioretinitis is diagnosed. Ocular toxoplasmosis appears as white retinal lesions with little associated hemorrhage; visual loss can occur initially.

Less frequent presentations in HIV-infected children with reactivated chronic toxoplasmosis include systemic toxoplasmosis, pneumonitis, hepatitis, and cardiomyopathy/myocarditis.[12,22]

Diagnosis

All infants whose mothers are both HIV-infected and seropositive for *Toxoplasma* should be evaluated for congenital toxoplasmosis **(AIII)**.[23] Congenital toxoplasmosis can be diagnosed by enzyme-linked immunoassay or an immunosorbent assay to detect *Toxoplasma*-specific immunoglobulin M (IgM), IgA, or IgE in neonatal serum within the first 6 months of life or persistence of specific immunoglobulin G antibody beyond age 12 months.[24-28] IgA may be more sensitive for detecting congenital infection than IgM or IgE.[25] However, approximately 20% to 30% of infants with congenital toxoplasmosis will not be identified during the neonatal period with IgA or IgM assays.[26]

Serologic testing is the major method of diagnosis, but interpretation of assays often is confusing and difficult. When considering a diagnosis of congenital toxoplasmosis, specialized reference laboratories can perform serology, isolation of organisms and polymerase chain reaction (PCR) and can offer assistance in interpreting results.[25,28]

Additional methods that can be used to diagnose infection in the newborn include isolation of the *Toxoplasma* parasite by mouse inoculation or inoculation in tissue cultures of cerebrospinal fluid (CSF), urine, placental tissue, amniotic fluid, or infant blood. *T. gondii* DNA can be detected by PCR performed on clinical specimens (e.g., white blood cells, CSF, amniotic fluid, tissue) in a reference laboratory.[25,26] The following evaluation should be undertaken for all newborns in whom a diagnosis of toxoplasmosis is suspected: ophthalmologic, auditory, and neurologic examinations; lumbar puncture; and imaging of the head (either CT or magnetic resonance imaging [MRI] scans) to determine whether hydrocephalus or calcifications are present.

CNS toxoplasmosis is presumptively diagnosed on the basis of clinical symptoms, serologic evidence of infection, and presence of a space-occupying lesion on imaging studies of the brain.[29] TE rarely has been reported in individuals without *Toxoplasma*-specific IgG antibodies; therefore, negative serology does not definitively exclude that diagnosis. Brain computer tomography (CT) that demonstrates multiple, bilateral, ring-enhancing lesions, especially in the basal ganglia and cerebral corticomedullary junction, would be typical of TE. Calcifications are more typical in congenital toxoplasmosis than in TE seen later in life. Magnetic resonance imaging (MRI) is more sensitive and will confirm basal ganglia lesions in most patients.[30] F-fluoro-2-deoxyglucose–positive emission tomography reportedly is helpful in adults in distinguishing *Toxoplasma* abscesses from primary CNS lymphoma, but the accuracy is not high, and this test is not widely available.

Definitive diagnosis of TE requires histologic or cytologic confirmation by brain biopsy, which may demonstrate leptomeningeal inflammation, microglial nodules, gliosis, and *Toxoplasma* cysts. Brain biopsy is reserved by some experts for patients who do not respond to specific therapy.

Prevention Recommendations

Preventing Exposure

All HIV-infected children and adolescents and their caregivers should be counseled about sources of *T. gondii* infection. They should be advised not to eat raw or undercooked meat, including undercooked lamb,

beef, pork, or venison **(BIII)**. All meat (lamb, beef, and pork) should be cooked to an internal temperature of 145°F for 3 minutes.[31] However, a study has found that *T. gondii* can survive at 64°C (147.2°F) for 3 minutes, so higher temperatures than this seem best for immunosuppressed patients.[32] Ground meat and wild game meat should be cooked to 71°C (160°F). Poultry should be cooked to 74°C (165°F). Hands should be washed after contact with raw meat and after gardening or other contact with soil; in addition, fruits and vegetables should be washed well before being eaten raw **(BIII)**. Stray cats should not be handled or adopted; a cat already in the household should be kept inside and the litter box changed daily, preferably by an HIV-uninfected individual who is not pregnant **(BIII)**. Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats **(BIII)**. Patients need not be advised to part with their cats or to have their cats tested for toxoplasmosis **(AII)**.

Preventing Disease

In the United States, routine *Toxoplasma* serologic screening of HIV-infected children whose mothers do not have toxoplasmosis is not recommended because of its low incidence. However, in regions with high incidence of *Toxoplasma* infection (≥1% per year), or for children immigrating from such regions, serologic testing can be selectively considered for HIV-infected children aged >12 months **(CIII)**. HIV-infected adolescents without previous *Toxoplasma* infection should undergo serologic testing **(CIII)**. *Toxoplasma*-seronegative adults and adolescents who are not taking *Pneumocystis* pneumonia (PCP) prophylaxis known to be active against TE should be retested for IgG antibody to *Toxoplasma* if their CD4 cell counts decline to <100 cells/mm^3 to determine whether they have seroconverted to *Toxoplasma*.

Toxoplasma-seropositive adolescents and adults who have CD4 cell counts <100 cells/mm^3 should be given prophylaxis against TE.[33] Specific levels of immunosuppression that increase the risk of TE in children are less well defined. *Toxoplasma*-seropositive children with CD4 percentages <15% should be given prophylaxis against TE **(AIII)**. For children aged ≥6 years, the same absolute CD4 count level used for HIV-infected adults can be used **(AIII)**.

In HIV-infected adolescents and adults, the double-strength-tablet daily dose of trimethoprim-sulfamethoxazole (TMP-SMX) recommended as the preferred regimen for PCP prophylaxis is effective TE prophylaxis **(AII)**.[33] Data from case series in children and from trials in adults support this as the preferred regimen in children using age-based dosing (See Table: Dosing Recommendations for the Prevention and Treatment of *Toxoplasma gondii*) **(BIII)**. TMP-SMX, one double-strength tablet 3 times weekly (or 3 consecutive days a week), is an alternative **(BIII)**. If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine, which also is effective against PCP **(BI*)**.[34,35] Atovaquone with or without pyrimethamine also can be considered **(CIII)**. Single-drug prophylaxis with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended **(AIII)**. Aerosolized pentamidine does not protect against TE and is not recommended.[33,36] Severely immunosuppressed children who are not receiving TMP-SMX or atovaquone who are seropositive for *Toxoplasma* should be given prophylaxis for both PCP and toxoplasmosis (i.e., dapsone plus pyrimethamine) **(BIII)**.

Discontinuing Primary Prophylaxis

Multiple observational studies[37-39] and two randomized trials[40,41] have reported that primary prophylaxis can be discontinued with minimal risk of TE in patients who have responded to cART with an increase in CD4 cell count to ≥200 cells/mm^3 for >6 months. Although patients with CD4 cell counts of <100 cells/mm^3 are at greatest risk of TE, the risk of TE when CD4 cell counts increase to 100 to 200 cells/mm^3 has not been studied as rigorously as an increase to >200 cells/mm^3. Thus, the recommendation for adults and adolescents specifies discontinuing prophylaxis after an increase to >200 cells/mm^3. Discontinuing primary TE prophylaxis when CD4 cell counts have increased to >200 cells/mm^3 is recommended because prophylaxis adds limited disease prevention for toxoplasmosis and because discontinuing drugs reduces pill burden, the potential for drug toxicity, drug interactions, selection of drug-resistant pathogens, and cost. Data do not exist on the safety of discontinuing primary TE prophylaxis for HIV-infected children whose immunologic status improves on cART.

Data on adults suggest discontinuation of TMP-SMX may be safe once a child responds to cART with a sustained rise in CD4 percentage above 15%; for children aged ≥6 years, the same CD4 cell count used for HIV-infected adults can be used **(BIII)**. A sustained response in children has been defined as a CD4 count or percentage above the threshold level for >3 consecutive months after receiving cART for >6 months.

Prophylaxis should be reintroduced in HIV-infected adults **(AIII)**, adolescents **(AIII)**, and children ≥6 years old **(BIII)** if the CD4 cell count decreases to <100 to 200 cells/mm^3 or the CD4 percentage falls below 15% for HIV-infected children aged <6 years **(BIII)**.

Treatment Recommendations

Treating Disease

Pregnant women with suspected or confirmed primary toxoplasmosis and newborns with possible or documented congenital toxoplasmosis should be managed in consultation with an appropriate infectious disease specialist. Although controversy exists about the efficacy of treating pregnant women who have acute toxoplasmosis in an attempt to prevent infection of the fetus,[42] most experts would recommend such therapy **(BII)**.[23] Empiric therapy should be strongly considered for newborns of HIV-infected mothers who had symptomatic or asymptomatic primary Toxoplasma infection during pregnancy, regardless of whether treatment was administered during pregnancy **(BIII)**.

The preferred treatment for congenital toxoplasmosis is pyrimethamine combined with sulfadiazine, with supplementary leucovorin (folinic acid) to minimize pyrimethamine-associated hematologic toxicity **(AII)**.[20,43] The preferred treatment for acquired toxoplasmosis in HIV-infected children is sulfadiazine plus pyrimethamine and leucovorin **(AI*)**. Please refer to http://www.daraprimdirect.com for information regarding access to pyrimethamine. If pyrimethamine is unavailable, clinicians may substitute age-appropriate-dosed trimethoprim-sulfamethoxazole in place of the combination of sulfadiazine, pyrimethamine, and leucovorin. Although the optimal duration of therapy is undefined, the recommended duration of treatment for congenital toxoplasmosis in HIV-uninfected infants is 12 months **(AII)**.[43] Older HIV-infected children with acquired CNS, ocular, or systemic toxoplasmosis should be treated with pyrimethamine and leucovorin plus sulfadiazine **(AI*)**. Acute therapy should be continued for 6 weeks, assuming clinical and radiologic improvement **(BII*)**. Longer courses of treatment may be required for extensive disease or poor response after 6 weeks. The primary alternative for sulfadiazine in patients who develop sulfonamide hypersensitivity is clindamycin, administered with pyrimethamine and leucovorin **(AI*)**. Azithromycin instead of clindamycin also has been used with pyrimethamine and leucovorin in sulfa-allergic adults, but this regimen has not been studied in children. Extrapolation of doses used in adults corresponds to a dose of 20 mg/kg given every 24 hours (maximum 1,000 mg) but this dose has not been evaluated in children.

Another alternative in adults is atovaquone plus pyrimethamine and leucovorin, or atovaquone with sulfadiazine alone, or atovaquone as a single agent in patients intolerant to both pyrimethamine and sulfadiazine; however, these regimens have not been studied in children **(BII*)**. In adults, atovaquone is dosed at twice the total daily dose used for PCP prophylaxis and is divided into four doses per day, but such dosing for treatment of acquired toxoplasmosis in children has not been evaluated. In a small (77 subjects) randomized trial in adults, TMP-SMX was reported to be effective and better tolerated than pyrimethamine-sulfadiazine.[44] Others have reported similar efficacy in open-label observational studies.[45] However, this has not yet been studied in children.

For isolated ocular toxoplasmosis in immunocompetent hosts, TMP-SMX alone is as effective as pyrimethamine-sulfadiazine.[46] However, these data have not been duplicated in HIV-infected patients; therefore, this regimen cannot be recommended for this group of patients.

Based upon treatment of congenital toxoplasmosis in HIV-uninfected children, corticosteroids such as dexamethasone and prednisone are recommended for all HIV-infected children with CNS disease when CSF protein is highly elevated (i.e., >1,000 mg/dL) or who have focal lesions with substantial mass effects **(BIII)**.

Because of the potential immunosuppressive effects of steroids, they should be discontinued as soon as possible.

Anticonvulsants should be given to children with TE who have a history of seizures **(AIII)** but should not be administered prophylactically to children without a history of seizures **(BIII)**. Anticonvulsants, if administered, should be continued at least through acute therapy.

Although the initiation of cART aids in the treatment of many opportunistic infections and malignancies, it has not been definitively shown to improve the outcome of TE therapy.

Monitoring and Adverse Events, Including IRIS

Children with TE should be routinely monitored for clinical and radiologic improvement and for adverse effects of treatment; changes in antibody titers are not useful for monitoring responses to therapy.

Toxoplasmosis-associated immune reconstitution inflammatory syndrome (IRIS) has been described rarely in HIV-infected adults and has not been described in HIV-infected children, although it could presumably occur.[47,48] IRIS in HIV-infected pregnant women may pose additional risk to the fetuses[49] although any unique risk for pregnant women co-infected with HIV and *Toxoplasma* has not been defined.

Pyrimethamine can be associated with rash (including Stevens-Johnson syndrome) and nausea. The primary toxicity of pyrimethamine is reversible bone marrow suppression (i.e., neutropenia, anemia, and thrombocytopenia). A complete blood count should be performed at least weekly in children who are on daily pyrimethamine and at least monthly in those on less-than-daily dosing **(AIII)**. Leucovorin (folinic acid) always should be administered with pyrimethamine; increased doses of leucovorin may be required in the event of marrow suppression. Because of the long half-life of pyrimethamine, leucovorin should be continued 1 week after pyrimethamine has been discontinued.

Adverse effects of sulfadiazine include rash, fever, leukopenia, hepatitis, gastrointestinal (GI) symptoms (e.g., nausea, vomiting, diarrhea), and crystalluria. Clindamycin can be associated with fever, rash, and GI symptoms (e.g., nausea; vomiting, and diarrhea, and including pseudomembranous colitis) and hepatotoxicity.

Drug interactions between anticonvulsant and antiretroviral drugs should be evaluated. Patients receiving corticosteroids should be closely monitored for development of other opportunistic infections.

Managing Treatment Failure

Brain biopsy should be considered in the event of early clinical or radiologic neurologic deterioration despite adequate empiric treatment or in children who do not clinically respond to anti-*Toxoplasma* therapy after 10 to 14 days. In children who undergo brain biopsy and have confirmed histopathologic evidence of TE despite treatment, a switch to an alternative regimen as previously described should be considered **(BIII)**.

Preventing Recurrence

Patients who have completed initial therapy for acquired TE should be given suppressive therapy (i.e., secondary prophylaxis or chronic maintenance therapy) **(AI*)**[50,51] until immune reconstitution occurs with cART. The combination of pyrimethamine, sulfadiazine, and leucovorin is highly effective for this purpose **(AI*)**. A commonly used regimen for patients who cannot tolerate sulfa drugs is pyrimethamine plus clindamycin with leucovorin **(BI*)**; however, only the combination of pyrimethamine plus sulfadiazine provides protection against PCP as well. Data on adults indicate atovaquone with or without pyrimethamine also can be considered for children **(CIII)**. Limited data support the use of TMP-SMX for secondary prophylaxis;[52] this regimen should be used only for patients who do not tolerate pyrimethamine plus sulfadiazine or pyrimethamine plus clindamycin **(CIII)** or if pyrimethamine is unavailable.

Discontinuing Secondary Prophylaxis

Adults and adolescents receiving secondary prophylaxis for acquired TE are at low risk of recurrence of TE when they have successfully completed their initial therapy, continue to have no signs or symptoms of TE, and

have a sustained increase in CD4 cell count of >200 cells/mm^3 after cART (i.e., >6 months).[38,39,41,53,54] Discontinuing chronic maintenance therapy in HIV-infected adolescents and adults who meet these criteria is a reasonable consideration. The highest risk of relapse appears to occur within the first 6 months after stopping secondary prophylaxis. Some specialists would obtain an MRI of the brain as part of their evaluation to determine whether discontinuing therapy is appropriate. The safety of discontinuing secondary prophylaxis after immune reconstitution with cART in children has not been studied extensively. However, given the data in adults, clinicians caring for HIV-infected children aged 1 to <6 years can consider discontinuing secondary prophylaxis against *T. gondii* after they have completed TE therapy and ≥6 months of stable cART and are asymptomatic and once the CD4 percentage has risen to ≥15% for >6 consecutive months **(BIII)**. For children aged ≥6 years, the same CD4 cell count used in adults (CD4 count >200 cells/mm^3) also can be used **(BIII)**. Prophylaxis should be re-instituted if these parameters are not met.

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Dosing Recommendations for the Prevention and Treatment of Toxoplasmosis (page 1 of 3)

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	TMP-SMX 150/750 mg/m^2 body surface area once daily by mouth	For Children Aged ≥1 Month: • Dapsone 2 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) by mouth once daily, **plus** • Pyrimethamine 1 mg/kg body weight (maximum 25 mg) by mouth once daily, **plus** • Leucovorin 5 mg by mouth every 3 days For Children Aged 1–3 Months and >24 Months: • Atovaquone 30 mg/kg body weight by mouth once daily Children Aged 4–24 Months: • Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) by mouth once daily, **plus** • Leucovorin 5 mg by mouth every 3 days Acceptable Alternative Dosage Schedules for TMP-SMX: • TMP-SMX 150/750 mg/m^2 body surface area per dose once daily by mouth 3 times weekly on 3 consecutive days per week • TMP-SMX 75/375 mg/m^2 body surface area per dose twice daily by mouth every day • TMP-SMX 75/375 mg/m^2 body surface area per dose twice daily by mouth 3 times weekly on alternate days	Primary Prophylaxis Indicated For: *IgG Antibody to Toxoplasma and Severe Immunosuppression:* • HIV-infected children aged <6 years with CD4 percentage <15%; HIV-infected children aged ≥6 years with CD4 count <100 cells/mm^3 Criteria for Discontinuing Primary Prophylaxis: **Note:** Do not discontinue in children aged <1 year • After ≥6 months of cART, **and** • Aged 1 to <6 years; CD4 percentage is ≥15% for >3 consecutive months • Aged ≥6 years; CD4 count >200 cells/mm^3 for >3 consecutive months Criteria for Restarting Primary Prophylaxis: • Aged 1 to <6 years with CD4 percentage <15% • Aged ≥6 years with CD4 count <100 to 200 cells/mm^3
Secondary Prophylaxis (Suppressive Therapy)	• Sulfadiazine 42.5–60 mg/ kg body weight per dose twice daily* (maximum 2–4 g per day) by mouth, **plus** • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) by mouth once daily, **plus** • Leucovorin 5 mg by mouth once every 3 days	• Clindamycin 7–10 mg/kg body weight per dose by mouth 3 times daily, **plus** • Pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) by mouth once daily, plus • Leucovorin 5 mg by mouth once every 3 days Children Aged 1–3 Months and >24 Months: • Atovaquone 30 mg/kg body weight by mouth once daily • Leucovorin, 5 mg by mouth every 3 days • TMP-SMX, 150/750 mg/m^2 body surface area once daily by mouth	Secondary Prophylaxis Indicated: • Prior toxoplasmic encephalitis **Note:** Alternate regimens with very limited data in children. TMP-SMX only to be used if patient intolerant to other regimens Criteria for Discontinuing Secondary Prophylaxis *If All of the Following Criteria are Fulfilled:* • Completed ≥6 months of cART, completed initial therapy for TE, asymptomatic for TE, **and**

Dosing Recommendations for the Prevention and Treatment of Toxoplasmosis (page 2 of 3)

Indication	First Choice	Alternative	Comments/Special Issues
Secondary Prophylaxis (Suppressive Therapy), continued		Children Aged 4–24 Months: • Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/m^2 body surface area (maximum 25 mg) by mouth once daily, **plus** • Leucovorin, 5 mg by mouth every 3 days • TMP-SMX, 150/750 mg/m^2 body surface area once daily by mouth	• Aged 1 to < 6 years; CD4 percentage ≥15% for >6 consecutive months • Aged ≥6 years; CD4 cell count >200 cells/mm^3 for >6 consecutive months Criteria For Restarting Secondary Prophylaxis: • Aged 1 to <6 years with CD4 percentage <15% • Aged ≥6 years with CD4 cell count <200 cells/mm^3
Treatment	Congenital Toxoplasmosis: • Pyrimethamine loading dose—2 mg/kg body weight by mouth once daily for 2 days, then 1 mg/kg body weight by mouth once daily for 2–6 months, then 1 mg/kg body weight by mouth 3 times weekly, **plus** • Leucovorin (folinic acid) 10 mg by mouth or IM with each dose of pyrimethamine, **plus** • Sulfadiazine 50 mg/kg body weight by mouth twice daily *Treatment Duration:* • 12 months Acquired Toxoplasmosis *Acute Induction Therapy (Followed by Chronic Suppressive Therapy):* • Pyrimethamine: loading dose—2 mg/kg body weight (maximum 50 mg) by mouth once daily for 3 days, then 1 mg/kg body weight (maximum 25 mg) by mouth once daily, **plus** • Sulfadiazine 25–50 mg/kg body weight (maximum 1–1.5 g/dose) by mouth per dose 4 times daily, **plus** • Leucovorin 10–25 mg by mouth once daily, followed by chronic suppressive therapy Treatment Duration (Followed by Chronic Suppressive Therapy): • ≥6 weeks (longer duration if clinical or radiologic disease	For Sulfonamide-Intolerant Patients: • Clindamycin 5–7.5 mg/kg body weight (maximum 600 mg/dose) by mouth or IV per dose given 4 times a day can be substituted for sulfadiazine combined with pyrimethamine and leucovorin	Congenital Toxoplasmosis: • For infants born to mothers with symptomatic *Toxoplasma* infection during pregnancy, empiric therapy of the newborn should be strongly considered irrespective of the mother's treatment during pregnancy. Acquired Toxoplasmosis: • Pyrimethamine use requires CBC monitoring at least weekly while on daily dosing and at least monthly while on less than daily dosing. • TMP-SMX—TMP 5 mg/kg body weight plus SMX 25 mg/kg body weight per dose IV or by mouth given twice daily has been used as an alternative to pyrimethamine-sulfadiazine in adults, but has not been studied in children. • Atovaquone (for adults, 1.5 g by mouth twice daily—double the prophylaxis dose) in regimens combined with pyrimethamine/ leucovorin, with sulfadiazine alone, or as a single agent in patients intolerant to both pyrimethamine and sulfadiazine, has been used in adults, but these regimens have not been studied in children. • Azithromycin (for adults, 900–1,200 mg/day, corresponding to 20 mg/kg/day in children) has also been used in adults combined with pyrimethamine-sulfadiazine, but has not been studied in children. • Corticosteroids (e.g., prednisone, dexamethasone) have been used in children with CNS disease when CSF protein is very elevated (>1,000 mg/dL) or there are focal lesions with significant mass effects, with discontinuation as soon as clinically feasible. • Anticonvulsants should be administered to patients with a history of seizures and

Dosing Recommendations for the Prevention and Treatment of Toxoplasmosis (page 3 of 3)

Indication	First Choice	Alternative	Comments/Special Issues
Treatment, continued	is extensive or response in incomplete at 6 weeks)		continued through the acute treatment; but should not be used prophylactically.

* **Note:** Sulfadiazine may be given as 2–4 equal doses per day as long as the total daily dose is 85–120 mg/kg body weight.

Key to Acronyms: cART = combination antiretroviral therapy; CBC = complete blood count; CD4 = CD4 T lymphocyte; CNS = central nervous system; CSF = cerebrospinal fluid; IgG = Immunoglobulin G; IM = intramuscular; IV = intravenous; TE = toxoplasmic encephalitis; TMP-SMX = trimethoprim-sulfamethoxazole