# Toxoplasmosis

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*Toxoplasma gondii* is a protozoan that can commonly cause asymptomatic infection, a mononucleosis-like syndrome, retinochoroiditis, or congenital infection in immunocompetent individuals, but it presents most often as toxoplasma encephalitis (TE) in people with HIV who are severely immunocompromised.[1-4] Toxoplasmosis in people with HIV appears to occur mainly due to reactivation of latent tissue cysts from a prior infection; primary infection is occasionally associated with acute cerebral or disseminated disease.

## Epidemiology

Primary infection occurs most commonly after consumption of undercooked meat, unwashed fruits or vegetables, water, or unpasteurized milk containing viable organisms, or ingesting oocysts that have been shed in cat feces and sporulated in the environment, a process that takes at least 24 hours. In up to 50% of individuals, primary infection can occur in the absence of conventional risk factors.[5] Infection can also be transmitted congenitally, or rarely following organ transplant or blood transfusion.[6-9] The organism is not transmitted through direct person-to-person contact.

Seroprevalence of anti-*Toxoplasma* antibody, indicating prior infection, can vary substantially within the United States based on geography and demographics, with an overall prevalence of approximately 11%, versus 40% to 80% in certain European, Latin American, Asian, and African countries.[10-12] In the era before antiretroviral therapy (ART), the 12-month incidence of TE was approximately 33% in patients with advanced immunodeficiency who were seropositive for *T. gondii* and not receiving prophylaxis with drugs active against the disease. A very low incidence of toxoplasmosis is seen in people with HIV who are seronegative for *T. gondii*. In these individuals, their toxoplasmosis presumably represents primary infection, reactivation of latent disease in individuals who cannot produce detectable antibodies, or the use of insensitive assays.[13,14]

## Clinical Manifestations

Clinical disease related to immunodeficiency is rare among people with HIV with CD4 T lymphocyte (CD4) cell counts >200 cells/mm$^3$. People with CD4 counts <50 cells/mm$^3$ are at greatest risk.[1,3,14,15] Among people with HIV, the most common clinical presentation of *T. gondii* infection is focal encephalitis, with subacute onset of headache, focal neurologic deficits (e.g., hemiparesis), and sometimes fever.[1,3,15] People with HIV also may present with non-focal encephalitis, with manifestations including isolated headache and generalized seizures.[16] Focal neurological abnormalities may be present on physical examination. In the absence of treatment, disease progression may result in seizures, stupor, coma, and death. Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain following intravenous contrast administration will typically show multiple contrast-enhancing lesions, with a predilection for the basal ganglia, often with edema and associated mass effect.[1,15,17-19] Toxoplasmosis can more rarely manifest as a single brain lesion or diffuse encephalitis without evidence of focal brain lesions on imaging studies.[16] The latter presentation tends to be rapidly progressive and fatal. Retinochoroiditis, pneumonia, adenopathy, and evidence of other multifocal organ system involvement can occur but are uncommon in people with HIV.

## Diagnosis

People with HIV and concomitant TE are usually seropositive for anti-toxoplasma immunoglobulin G (IgG) antibodies.[1,3,15,20] The absence of IgG antibody makes a diagnosis of toxoplasmosis unlikely but not impossible. Anti-toxoplasma immunoglobulin M (IgM) antibodies are usually absent and should not be requested unless primary infection is suspected. Quantitative antibody titers are not useful for diagnosis.

Definitive diagnosis of TE requires a compatible clinical syndrome, identification of one or more mass lesions by CT or MRI, and detection of the organism in a clinical sample. A presumptive diagnosis is based on a consistent clinical and radiographic presentation, presence of anti-*Toxoplasma* IgG antibodies, and response to anti-*Toxoplasma* therapy, but without detection of the organism. Most diagnoses are made either presumptively or based on a positive cerebrospinal fluid (CSF) toxoplasma polymerase chain reaction (PCR).

On imaging studies, toxoplasmosis presents as contrast-enhancing lesions (typically ring-enhancing), with a predilection for the basal ganglia. MRI has sensitivity superior to that of CT and should be obtained in patients with equivocal or negative CT studies. Positron emission tomography[18] or single-photon emission CT scanning[19] may be helpful in distinguishing between TE and primary central nervous system (CNS) lymphoma, but no imaging technique is completely specific. For TE, detection of the organism requires either a brain biopsy, most commonly stereotactic, or a positive CSF PCR test. Hematoxylin and eosin stains can be used for detection of *T. gondii* in biopsies, but sensitivity is significantly increased if immunoperoxidase staining is used and if experienced laboratories process the specimens.[21]

If safe and feasible, a lumbar puncture should be performed for *T. gondii* PCR, as well as for cytology, culture, cryptococcal antigen, and PCR for *Mycobacterium tuberculosis*, Epstein-Barr virus (EBV), and JC virus (JCV) depending on imaging findings. PCR for cytomegalovirus and varicella-zoster virus, as well as testing for syphilis, may also be considered. Detection of *T. gondii* by PCR in CSF has high specificity (96% to 100%), but low sensitivity (50%), especially once specific anti-*Toxoplasma* therapy has been started.[22-25]

The differential diagnosis of CNS lesions with mass effect in patients with AIDS most often includes primary CNS lymphoma, tuberculosis, and endemic fungal infection (e.g., cryptococcosis). Lymphoma can be indistinguishable from TE radiographically, both frequently presenting with ring-enhancing lesions, although lymphoma presents more often with a single lesion.[26] In the absence of immune reconstitution inflammatory syndrome (IRIS), progressive multifocal leukoencephalopathy (PML) can be distinguished based on imaging studies. PML lesions typically involve white matter rather than gray matter, are usually non-contrast-enhancing, and produce no mass effect. There are a large number of less common causes of focal neurologic disease in people with AIDS including Chagas disease, metastatic tumors, and pyogenic brain abscess, particularly in people who inject drugs.

Given the risks associated with a brain biopsy, and the difficulty in obtaining one at many centers, a presumptive diagnosis of TE is established based on an objective response to empiric therapy.[27] Brain biopsy is then reserved for patients who fail to respond to specific therapy, although earlier biopsy should be strongly considered if results from imaging, serology, or CSF PCR do not confirm toxoplasmosis or suggest an etiology other than toxoplasmosis. In patients with contrast-enhancing lesions, detection of EBV in the CSF by PCR should raise concern for CNS lymphoma, especially

when quantitative results show CSF levels above 10,000 EBV copies/mL; however, it is not diagnostic by itself.[28-30] In people with HIV receiving ART, PML-IRIS may also present with contrast-enhancing lesions, in which case JCV by PCR in CSF is highly suggestive of PML.[31]

## Preventing Exposure

People with HIV should be counseled regarding sources of *Toxoplasma* infection. Those with CD4 counts <200 cells/mm$^3$ should be tested for IgG antibody to *Toxoplasma* soon after they are diagnosed with HIV to detect latent infection with *T. gondii* (**BIII).**

To minimize risk of acquiring toxoplasmosis, people with HIV, especially those with CD4 counts <200 cells/mm$^3$, should be advised not to eat raw or undercooked meat, including undercooked lamb, beef, pork, or venison, and not to eat raw shellfish, including oysters, clams, and mussels **(BIII).** Lamb, beef, venison, and pork should be cooked to an internal temperature of 165 °F to 170 °F;[32] meat cooked until it is no longer pink inside usually has an internal temperature of 165 °F to 170 °F, and therefore, from a more practical perspective, satisfies this requirement. People with HIV should wash their hands after contact with raw meat and after gardening or other contact with soil; they should also wash fruits and vegetables well before eating them raw **(BIII).**

Cat owners with HIV whose CD4 counts are <200 cells/mm$^3$ and who are seronegative should be advised to have a nonpregnant person without HIV change the litter box daily. If a person with HIV must change the litter box themselves, they should wear gloves and wash their hands thoroughly afterward **(BIII).** They also should be encouraged to keep their cats inside and not to adopt or handle stray cats **(BIII).** Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats **(BIII).** People with HIV do not need to be advised to part with their cats or to have their cats tested for toxoplasmosis **(BIII).**

## Preventing Disease

### Recommendations for Preventing *Toxoplasma gondii* Encephalitis

| Preventing 1st Episode of *Toxoplasma gondii* Encephalitis (Primary Prophylaxis) |
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| Indications for Initiating Primary Prophylaxis |
| • *Toxoplasma* IgG positive patients with CD4 count <100 cells/mm$^3$ (AII) |
| Note: Listed regimens are also effective against PCP. |
| Preferred Regimen |
| • TMP-SMX one DS PO daily (AII) |
| Alternative Regimens |
| • TMP-SMX one DS PO three times weekly (BII), *or* |
| • TMP-SMX one SS PO daily (BIII), *or* |
| • Dapsone[a] 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly (BI), *or* |
| • (Dapsone[a] 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly (CI), *or* |
| • Atovaquone[b] 1,500 mg PO daily (CIII), *or* |

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|---|
| • (Atovaquone[b] 1,500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily (CIII)<br><br>Indication for Discontinuing Primary Prophylaxis<br><br>• CD4 count >200 cells/mm$^3$ for >3 months and sustained HIV RNA below limits of detection in response to ARV therapy (AI); *or*<br><br>• Can consider if CD4 count is 100–200 cells/mm$^3$ and HIV RNA remains below limits of detection for at least 3–6 months (BII)<br><br>Indication for Restarting Primary Prophylaxis<br><br>• CD4 count <100 cells/mm$^3$ (AIII)<br><br>• CD4 count 100–200 cells/mm$^3$ and HIV RNA above detection limits (AIII) |
| Pregnancy Considerations |
| Indication, drugs, and doses are the same as for nonpregnant individuals. |

[a] Whenever possible, patients should be tested for G6PD deficiency before administrating dapsone. Alternative agent should be used if the patient is found to have G6PD deficiency.

[b] Atovaquone should be taken with meals or nutritional supplement to ensure adequate oral absorption.

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; DS = double-strength; G6PD = glucose-6-phosphate dehydrogenase; IgG = immunoglobulin G; PCP = *Pneumocystis* pneumonia; PO = orally; SS = single-strength; TMP-SMX = trimethoprim-sulfamethoxazole

## *Indication for Primary Prophylaxis*

*Toxoplasma*-seropositive people who have CD4 counts <100 cells/mm$^3$ should receive prophylaxis against TE **(AII).**[33,34]

The preferred primary prophylaxis regimen is one double-strength tablet daily of TMP-SMX **(AII).** This is also the preferred prophylaxis regimen for *Pneumocystis jirovecii* pneumonia (PCP), which all people at risk for toxoplasmosis are also at risk for developing. TMP-SMX, one double-strength tablet three times weekly, is an alternative **(BII).** TMP-SMX, one single-strength tablet daily, is also an option **(BIII).** If TMP-SMX cannot be tolerated, the recommended alternative is dapsone plus pyrimethamine plus leucovorin, which also is effective against PCP (see table for rating based on dapsone and pyrimethamine doses).[35-37] Atovaquone with or without pyrimethamine plus leucovorin is active against PCP and can also be considered for toxoplasmosis **(CIII).** For people in whom other alternatives are not possible, pyrimethamine (plus leucovorin) alone may have some efficacy as primary prophylaxis **(CIII).**[14] Aerosolized pentamidine does not protect against TE and **is not recommended** for anti-*Toxoplasma* prophylaxis **(AI).**[33,38]

## *Discontinuing Primary Prophylaxis*

Prophylaxis against TE should be discontinued in adults and adolescents with HIV receiving ARV therapy with sustained suppression of plasma HIV RNA levels below the detection limits of available assays whose CD4 counts increase to >200 cells/mm$^3$ for more than 3 months **(AI).**[39-43] In this setting primary TE prophylaxis should be discontinued because it adds little value in preventing toxoplasmosis and increases pill burden, potential for drug toxicity and interaction, likelihood of development of drug-resistant pathogens, and cost.

A combined analysis of 10 European cohorts found a low incidence of TE in patients with CD4 counts between 100 and 200 cells/mm$^3$, who were receiving ARVs and had HIV RNA plasma viral loads <400 copies/mL, and who had stopped or never received TE prophylaxis; this suggests that primary TE prophylaxis can be safely discontinued in patients with CD4 counts 100 to 200 cells/mm$^3$ and HIV plasma RNA levels below limits of detection with commercial assays.[44] Similar observations have been made with regard to stopping primary or secondary prophylaxis for PCP.[44-46] Data on which to base specific recommendations are inadequate, but one approach would be to stop primary prophylaxis in patients with CD4 counts of 100 to 200 cells/mm$^3$ if HIV plasma RNA levels remain below limits of detection for at least 3 to 6 months **(BII).**[44]

## Treating Disease

### Recommendations for Treating *Toxoplasma gondii* Encephalitis

| Treating *Toxoplasma gondii* Encephalitis |
|---|
| Preferred Regimens for Acute Infection<br>• Pyrimethamine 200 mg PO once, followed by weight-based dosing (AI):<br>  o Body weight ≤60 kg: pyrimethamine 50 mg PO daily + sulfadiazine 1,000 mg PO every 6 hours + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or twice daily)<br>  o Body weight >60 kg: pyrimethamine 75 mg PO daily + sulfadiazine 1,500 mg PO every 6 hours + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or twice daily)<br>*or*<br>• TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) twice daily (AII)<br>Note: If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, TMP-SMX should be used in place of pyrimethamine-sulfadiazine (AII).<br>Alternative Regimens for Acute Infection<br>• (Pyrimethamine + leucovorin)[c] plus clindamycin 600 mg IV or PO every 6 hours (AI); preferred alternative for patients intolerant of sulfadiazine or who do not respond to pyrimethamine[b]-sulfadiazine; must add additional agent for PCP prophylaxis (AII), *or*<br>• Atovaquone[b] 1,500 mg PO twice daily + (pyrimethamine +leucovorin)[c] (BII), *or*<br>• Atovaquone[b] 1,500 mg PO twice daily + sulfadiazine[d] (BII), *or*<br>• Atovaquone[b] 1,500 mg PO twice daily (BII)<br>• For patients with a history of sulfa allergy, rapid sulfa desensitization may be attempted using one of several published strategies (BI).<br>• During the desensitization phase, atovaquone 1,500 mg PO should be administered twice daily until therapeutic doses of TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) twice daily are achieved (CIII).<br>Total Duration for Treating Acute Infection<br>• At least 6 weeks (BII); longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks<br>• After completion of the acute therapy, all patients should be continued on chronic maintenance therapy as outlined below. |

Chronic Maintenance Therapy for *Toxoplasma gondii* Encephalitis

*Preferred Regimens*

- Pyrimethamine 25–50 mg PO daily + sulfadiazine 2,000–4,000 mg PO daily (in 2 to 4 divided doses) + leucovorin 10–25 mg PO daily (AI), *or*
- TMP-SMX DS one tablet twice daily (AII)

*Alternative Regimens*

- (Pyrimethamine 25–50 mg + leucovorin 10–25 mg) PO daily plus clindamycin 1,800 mg PO daily dose (in 3 or 4 divided doses) (BI); must add additional agent to prevent PCP (AII), *or*
- Atovaquone[b] 750–1,500 mg PO twice daily + (pyrimethamine 25 mg + leucovorin 10 mg) PO daily (BII), *or*
- Atovaquone[b] 750–1,500 mg PO twice daily + sulfadiazine 2,000–4,000 mg PO daily (in 2 to 4 divided doses) (BII), *or*
- Atovaquone[b] 750–1,500 mg PO twice daily (BII)

*Criteria for Discontinuing Chronic Maintenance Therapy (BI)*

- Successfully completed initial therapy, *and*
- Asymptomatic of signs and symptoms of TE, *and*
- CD4 count >200 cells/mm$^3$ for >6 months in response to ARVs

*Criteria for Restarting Secondary Prophylaxis/Chronic Maintenance*

- CD4 count <200 cells/mm$^3$ regardless of HIV RNA level (AIII)

## Other Considerations

- Adjunctive corticosteroids (e.g., dexamethasone) should only be administered when clinically indicated to treat a mass effect associated with focal lesions or associated edema (BIII) or for control of clinically significant IRIS symptoms in conjunction with ART and anti-toxoplasma therapy (CIII); discontinue as soon as clinically feasible. For patients in whom the diagnosis of TE is presumptive based in part on clinical response, one needs to be careful as CNS lymphoma may also respond to steroids clinically and radiologically.
- Antiseizure medications should be administered to patients with TE and associated seizures (AII) and continued through at least the period of acute treatment (BII); antiseizure medications should not be used as prophylaxis in patients without seizures (BII).

## Pregnancy Considerations

Suspected or Confirmed Acute Toxoplasmosis During Pregnancy

*Initial Therapy (primary infection during pregnancy or symptomatic reactivation of* T. gondii *without encephalitis)*

- Initiation of therapy before 14 weeks of pregnancy: spiramycin administered orally at a dosage of 1.0 g (or 3 million U) every 8 hours (total dosage of 3 g or 9 million U per day) (AII)
- Initiation of therapy on or after 14 weeks of pregnancy: pyrimethamine (50 mg PO twice daily x 2 days, then 50 mg PO daily) + sulfadiazine (75 mg/kg PO x 1 day, then 50 mg/kg PO twice daily) + leucovorin (10–20 mg/day during and 1 week after pyrimethamine use) (AII)

*Fetal Assessment*

- Amniocentesis for toxoplasmosis PCR to be done at 18 weeks gestation or later (BIII)
- Fetal ultrasonography every 4 weeks until delivery (AIII)
- If no evidence of fetal infection (negative amniotic fluid PCR, no fetal ultrasonographic abnormalities), continue initial therapy.

Treatment of *Toxoplasma gondii* Encephalitis During Pregnancy

- Treatment regimen is the same as for nonpregnant individuals (BIII).
- In general, pyrimethamine should be avoided in the first trimester of pregnancy because of teratogenicity concerns, but in the case of TE, the benefit of using pyrimethamine to the pregnant individual outweighs the risk to the fetus.

Fetal Infection

*Criteria for Initiating Treatment for Fetal Infection*

- Positive amniotic fluid PCR, *and/or*
- Fetal ultrasonographic findings suggestive of congenital toxoplasmosis

*Treatment for Fetal Infection*

- Pyrimethamine + sulfadiazine + leucovorin until delivery (AII)

Note: If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, TMP-SMX DS one tablet twice daily plus spiramycin 1 g PO three times a day plus leucovorin 4 mg daily should be utilized in place of pyrimethamine-sulfadiazine (BII).

[a] Whenever possible, patients should be tested for G6PD deficiency before administrating dapsone. Alternative agent should be used if the patient is found to have G6PD deficiency.

[b] Atovaquone should be taken with meals or nutritional supplement to ensure adequate oral absorption.

[c] Pyrimethamine and leucovorin doses: Same doses and frequency as listed in Preferred Regimen for Acute Infection

[d] Sulfadiazine dose: Same as weight-based dose and frequency listed in Preferred Regimen for Acute Infection

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CNS = central nervous system; DS = double-strength; G6PD = glucose-6-phosphate dehydrogenase; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; PCP = *Pneumocystis* pneumonia; PCR = polymerase chain reaction; PO = orally; SMX = sulfamethoxazole; TE = toxoplasma encephalitis; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

For many years, the initial therapy of choice for TE has been the combination of pyrimethamine plus sulfadiazine plus leucovorin **(AI).**[2,47-49] Pyrimethamine penetrates the brain parenchyma efficiently even in the absence of inflammation.[50] Leucovorin reduces the likelihood of hematologic toxicities associated with pyrimethamine therapy.[51] Pyrimethamine, however, has become extremely expensive and can be difficult to obtain in the United States.

TMP-SMX has been used with increasing frequency as a preferred regimen **(AII),** although large, randomized trials comparing TMP-SMX to pyrimethamine plus sulfadiazine have not been performed. In a small (77 patients) randomized trial, TMP-SMX was reported to be as effective and better tolerated than pyrimethamine-sulfadiazine.[52] Others have reported similar efficacy of TMP-SMX to pyrimethamine plus sulfadiazine in open-label observational studies.[53,54] A recent meta-analysis found that TMP-SMX was as effective as pyrimethamine plus sulfadiazine, but was associated with less toxicity.[55] If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, TMP-SMX should be utilized **(AII).**

Pyrimethamine plus leucovorin plus clindamycin[47,48] is the preferred alternative regimen for patients with TE who cannot tolerate sulfa drugs or do not respond to first-line therapy **(AI).** This combination, however, does not prevent PCP, therefore additional PCP prophylaxis must be administered when it is used **(AII)** (see discussion under Preventing Recurrence).[56]

For patients with a history of sulfa allergy, rapid sulfa desensitization may be attempted using one of several published strategies **(BI).**[57-62] During the desensitization period, atovaquone with or without pyrimethamine should be administered until therapeutic doses of TMP-SMX are achieved **(CIII).**

No well-studied options exist for patients who cannot take an oral regimen. No parenteral formulation of pyrimethamine exists and the only widely available parenteral sulfonamide is the sulfamethoxazole component of TMP-SMX. Some specialists will use parenteral TMP-SMX **(BII)** or oral pyrimethamine plus parenteral clindamycin **(CIII)** as initial treatment in severely ill patients who require parenteral therapy**.**

Atovaquone (with meals or oral nutritional supplements) plus pyrimethamine plus leucovorin, atovaquone plus sulfadiazine, or (for patients intolerant of both pyrimethamine and sulfadiazine) atovaquone as a single agent also have been shown to be effective in treating TE **(BII).**[63,64,65] However, the relative efficacy of atovaquone-containing regimens compared with other regimens is unknown. Clinicians should be aware that the absorption of the drug varies substantially from patient to patient; plasma levels >18.5 µg/mL are associated with an improved response rate but atovaquone therapeutic drug monitoring is not routinely available.[64-66]

The following regimens have been reported to have activity in treatment of TE in small cohorts of patients or in case reports of one or several patients: azithromycin plus pyrimethamine plus leucovorin **(CII)**[67,68]; clarithromycin plus pyrimethamine plus leucovorin **(CIII)**[69]; 5-fluorouracil plus clindamycin **(CIII)**[70]; dapsone plus pyrimethamine plus leucovorin **(CIII)**[71]; and minocycline or doxycycline combined with either pyrimethamine plus leucovorin, sulfadiazine, or clarithromycin **(CIII).**[72,73] There is rarely a reason to use one of these regimens.

Clinical response to acute therapy occurs in ~90% of patients with TE within 14 days of initiating appropriate anti-*Toxoplasma* treatment.[2] The reasons why some patients fail therapy are not clearly proven; whether such failures are due to poor adherence, other host factors, or antimicrobial resistance has not been well delineated. Acute therapy for TE should be continued for 6 weeks, if there is clinical and radiologic improvement **(BII).**[1-4] Longer courses may be necessary if clinical or radiologic disease is extensive or response is incomplete at 6 weeks. After completion of the acute therapy, all patients should be continued on chronic maintenance therapy as outlined below (see Preventing Recurrence section below). The radiologic goals for treatment include resolution of the lesion(s) in terms of size, contrast enhancement, and associated edema, although residual contrast-enhancing lesions may persist for prolonged periods, especially in people with HIV receiving ARVs.[74]

## *Adjunctive Therapies*

Adjunctive corticosteroids such as dexamethasone should only be used for treatment of patients with TE when they are clinically indicated to treat a mass effect associated with focal lesions or associated edema **(BIII).** In those treated with corticosteroids, caution may be needed in diagnosing CNS toxoplasmosis on the basis of treatment response, since primary CNS lymphoma may respond clinically and radiographically to corticosteroids alone; these patients should be monitored carefully as corticosteroids are tapered. In addition, corticosteroids should be discontinued as soon as clinically feasible because of their potential to cause immunosuppression. Patients receiving corticosteroids should be monitored closely for development of other opportunistic infections (OIs), including cytomegalovirus retinitis and tuberculosis.

Antiseizure medications should be administered to patients with TE associated with seizures **(AII)** but **should not be administered** prophylactically to patients **without seizures (BII).** Anticonvulsants, if indicated, should be continued at least through the period of acute therapy **(BII).**

## *Special Considerations Regarding ART Initiation*

There are no data on which to base a recommendation regarding when to start ARV therapy in people with HIV and TE. However, many physicians would initiate ARV therapy within 2 to 3 weeks after the diagnosis of toxoplasmosis, based on the significantly lower incidence of AIDS progression or death (a secondary study endpoint) seen in the early ARV therapy arm of a controlled trial of 282 patients with OIs other than tuberculosis (only 5% of whom had toxoplasmosis) who were randomized to early (median 12 days after initiation of OI therapy) versus deferred (median 45 days) initiation of ARV therapy.[75]

### IRIS

IRIS associated with TE has been reported but appears to be rare (~5% in one report).[76-78] Most cases develop as paradoxical worsening with increase in the size and number of lesions, peri-lesional edema, and an increase in contrast enhancement on MRI.[77,79,80] As for IRIS with other infections, corticosteroid therapy, dosed to control symptoms, can be administered in patients with clinically significant symptoms in conjunction with ARVs and anti-*Toxoplasma* therapy **(CIII).**

### *Monitoring of Response to Therapy and Adverse Events (Including IRIS)*

Changes in antibody titers are not useful for monitoring responses to therapy. People with HIV with TE should be monitored routinely for adverse events and clinical and radiologic improvement **(AIII).**

Neurological improvement will occur by 14 days in over 90% of patients[2]; if no improvement is seen by that time, other diagnoses should be considered. Repeat imaging can be considered at 3 and 6 weeks, or sooner for clinical deterioration.[2] After 6 weeks, maintenance therapy at ~50% of treatment doses should be initiated assuming a clinical response has been seen.

Common pyrimethamine toxicities such as rash, nausea, and bone marrow suppression (neutropenia, anemia, and thrombocytopenia) often can be reversed by increasing the leucovorin dose to 10, 25, or 50 mg four times daily **(CIII).** Common sulfadiazine toxicities include rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhea, renal insufficiency, and crystalluria. Common clindamycin toxicities include fever, rash, nausea, diarrhea (including pseudomembranous colitis or diarrhea related to *Clostridium difficile* toxin), and hepatotoxicity. Common TMP-SMX toxicities include rash, fever, leukopenia, thrombocytopenia, and hepatotoxicity. Common atovaquone toxicities include nausea, vomiting, diarrhea, rash, headache, hepatotoxicity, and fever. Drug interactions between certain anticonvulsants (e.g., phenytoin, phenobarbital, carbamazepine), dexamethasone and antiretroviral (ARV) agents should be evaluated carefully; if necessary, doses should be adjusted, or alternative anticonvulsants or ARV agents should be used.

## *Managing Treatment Failure*

A brain biopsy should be strongly considered in patients who did not have an initial biopsy prior to therapy and who fail to respond to initial therapy for TE **(BII)** as defined by clinical or radiologic deterioration during the first week despite adequate therapy, or who do not show clinical

improvement within 10 to 14 days. A switch to an alternative regimen, as previously described, should be considered for those who undergo brain biopsy and have confirmed histopathologic evidence of TE, or who have a CSF PCR positive for *T. gondii* **(BIII).** In patients who adhere to their regimens, disease recurrence is unusual in the setting of chronic maintenance therapy after an initial clinical and radiographic response.

## Preventing Recurrence

### *When to Start Chronic Maintenance Therapy*

Patients who have completed initial therapy for TE should be given chronic maintenance therapy to suppress infection **(AI)**[47,48] until immune reconstitution occurs as a consequence of ARV therapy. The combination of pyrimethamine plus sulfadiazine plus leucovorin is highly effective as suppressive therapy for patients with TE **(AI)** and provides protection against PCP **(AII).** Although sulfadiazine is routinely dosed as a four-times-a-day regimen, a pharmacokinetic study suggests bioequivalence for the same total daily dose when given either twice or four times a day,[81] and limited clinical experience suggests that twice-daily dosing is effective.[82]

For patients being treated with TMP-SMX, this drug should be continued as chronic maintenance at a reduced dose of one double-strength tablet twice daily **(AII).**[52] A small, uncontrolled study in patients who had been receiving ART for a median of 13 months suggested that TMP-SMX could be used as a suppressive regimen in place of pyrimethamine-sulfadiazine or pyrimethamine-clindamycin to reduce pill burden.[83]

Pyrimethamine plus leucovorin plus clindamycin is commonly used as suppressive therapy for patients with TE who cannot tolerate sulfa drugs **(BI).** Because of the high failure rate observed with lower doses,[47] a dose of 1,800 mg clindamycin daily in 3 or 4 divided doses is recommended. Because this regimen does not provide protection against PCP **(AII),**[56] an additional agent, such as dapsone or aerosol pentamidine, must be used. Atovaquone also is active against both TE[65,66] and PCP[84] and can be used alone, with sulfadiazine, or with pyrimethamine and leucovorin in patients with TE **(BII).**

### *When to Stop Chronic Maintenance Therapy*

Chronic maintenance therapy for TE can be discontinued in adults and adolescents with HIV, if they have successfully completed initial therapy for TE, remain asymptomatic with regard to signs and symptoms of TE, and have an increased CD4 count to >200 cells/mm$^3$ for >6 months in response to ARV therapy **(BI),** although occasional recurrences have been reported.[40,43,85,86] As part of the evaluation to determine whether discontinuation of therapy is appropriate, some specialists recommend obtaining an MRI of the brain to assess for resolution of brain lesions, although residual contrast-enhancing lesions can be seen for prolonged periods in some ARV-treated patients.

### *When to Restart Primary Prophylaxis or Maintenance Therapy*

Primary prophylaxis should be reintroduced if the CD4 count decreases to <100 cells/mm$^3$ **(AIII)** regardless of the HIV plasma viral load. Based on results from the COHERE study, an observational study of multiple cohorts, primary prophylaxis may not need to be restarted in patients with CD4 counts of 100 to 200 cells/mm$^3$ who have had HIV plasma RNA levels below limits of detection for at least 3 to 6 months **(BII).**[44,45] For patients with CD4 counts of 100 to 200 cells/mm$^3$ with HIV plasma viral load above detection limits of the utilized assay, PCP prophylaxis should be

reintroduced, and most, but not all, regimens will provide prophylaxis for toxoplasmosis as well **(AIII).**

Because there are no published data examining the risk of recurrence in patients stopping chronic maintenance therapy for TE when the CD4 count is between 100 and 200 cells/mm$^3$, and recurrent TE can be debilitating and potentially life-threatening, maintenance therapy should be reintroduced if the CD4 count decreases to <200 cells/mm$^3$ **(AIII)** regardless of the HIV plasma viral load.[87]

## Special Considerations During Pregnancy

### *Diagnosis During Pregnancy*

Documentation of baseline *T. gondii* serologic status (IgG only) should be obtained in people with HIV who become pregnant because of concerns regarding congenital toxoplasmosis. Although perinatal transmission of *T. gondii* normally occurs only with acute infection in the immunocompetent host, case reports have documented transmission with reactivation of chronic infection in pregnant people with HIV with severe immunosuppression.[88,89] Knowing toxoplasmosis sero-status at the beginning of pregnancy may be helpful in delineating future risks and interpreting serologic testing performed later in pregnancy should there be heightened concerns for maternal infection and/or fetal transmission.

*Toxoplasma* infection during pregnancy is usually asymptomatic. Non-specific symptoms may include fever, fatigue, headache, and myalgia after a 5- to 23-day incubation period. In the setting of parasitemia during pregnancy, the placenta may become infected and result in fetal infection. The risk of congenital toxoplasmosis (infection of the fetus) is highest in the setting of a primary infection during pregnancy as compared to reactivation. While the risk of transmission to the fetus increases with gestational age, with the highest risk in the third trimester, the sequelae to the fetus are more severe when toxoplasmosis is acquired early in gestation.[90,91]

Toxoplasmosis diagnostic considerations are not affected by pregnancy. Primary *T. gondii* infection can typically be distinguished from chronic infection with the use of multiple serologic assays, including IgG, IgM, immunoglobulin A, and immunoglobulin E antibodies; IgG avidity; and the differential agglutination tests.[92,93] Because serologic testing is often difficult to interpret and prompt treatment and counseling is particularly important during pregnancy, people with HIV with suspected primary *T. gondii* infection during pregnancy should be managed in consultation with a maternal-fetal medicine specialist where available. The care team may elect to access specialized laboratory testing[93,94] (e.g., the Palo Alto Medical Foundation Toxoplasmosis Serology Laboratory [PAMF-TSL], Palo Alto, CA, at 650-853-4828 and toxolab@pamf.org; and the National Collaborative Chicago-based Congenital Toxoplasmosis Study [NCCCTS], Toxoplasmosis Center, Chicago, IL, 773-834-4130, eFax 773-834 3577 and rmcleod@midway.uchicago.edu).

### *Screening*

The value of routine toxoplasmosis screening programs is debated in the United States but generally accepted in other countries. In countries such as France where pregnant people are universally screened and treated, offspring who acquire toxoplasmosis are reported to have primarily mild disease and rarely severe disease. In contrast, in countries without a universal screening program (e.g., United States), offspring who acquire toxoplasmosis mostly present with severe disease.[95]

Toxoplasmosis is not a nationally notifiable illness, is only reportable in eight states, and case definitions vary.[12]

## *Preventing Congenital Infection: Initial Therapy and Surveillance*

Pregnant people with HIV who have evidence of primary toxoplasmic infection, without TE, should be evaluated and managed during pregnancy in consultation with appropriate specialists **(BIII).** Recent studies support treatment of toxoplasmosis during pregnancy in an effort to decrease congenital transmission and reduce the severity of clinical signs in the offspring.[96-102]

In the setting of primary infection during pregnancy or symptomatic reactivation of *T. gondii*, initial therapy depends on the gestational age at time of acquisition/reactivation.

- For patients presumed to have acquired/reactivated infection at less than 14 weeks gestation, spiramycin is recommended to prevent congenital transmission **(AII).** Spiramycin is not commercially available in the United States. To obtain spiramycin, the provider must call the U.S. Food and Drug Administration directly (301-796-1400) after consultation with PAMF-TSL or NCCCTS (see Diagnosis During Pregnancy for contact information). A clinical pharmacist will assist with the proper paperwork.
- For patients presumed to have acquired/reactivated infection at 14 weeks gestation or beyond, pyrimethamine plus sulfadiazine plus leucovorin is recommended, as the risk of fetal transmission is higher **(AII).** If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, a combination of TMP-SMX, spiramycin, and leucovorin should be utilized in place of pyrimethamine-sulfadiazine **(BII).**[103,104]

For pregnant people with suspected primary or symptomatic reactivation of *T. gondii* during pregnancy, detailed ultrasound examination of the fetus specifically evaluating for hydrocephalus, cerebral calcifications, and growth restriction should be done monthly regardless of gestational age at the time of diagnosis **(AIII).**[93] In addition, patients should undergo an amniocentesis with PCR testing for *T. gondii* DNA in the amniotic fluid.[105] Amniocentesis does not appear to increase the risk of perinatal HIV transmission, particularly in people receiving ARV therapy.[106] Therefore, PCR of amniotic fluid can be considered during gestation in pregnant people on ARV therapy with serologic evidence of recently acquired *Toxoplasma* infection; people suspected to have reactivated their *Toxoplasma* latent infection during pregnancy; and those with ultrasound findings suggestive of fetal *T. gondii* infection **(BIII).**[93] In an effort to minimize false-negative results, amniotic fluid testing for *T. gondii* PCR should be avoided at less than 18-week gestation.[107]

## *Congenital Infection*

For patients whose evaluations do not suggest congenital infection (i.e., no ultrasound findings and negative amniotic fluid PCR), initial therapy should be continued until delivery. For patients started on spiramycin as initial therapy who are found to have a positive PCR in the amniotic fluid and/or ultrasound findings concerning for congenital transmission, therapy should be escalated to pyrimethamine/sulfadiazine/leucovorin **(AII),** or if pyrimethamine is unavailable, TMP-SMX, spiramycin, and leucovorin **(AII).**

Pediatric-care providers should be informed about birthing parents with HIV who have suspected or confirmed *T. gondii* infection to allow evaluation of their neonates for evidence of congenital infection **(AIII).**

## *Toxoplasma Encephalitis During Pregnancy*

Treatment of pregnant people with TE should be the same as in nonpregnant adults **(BIII),** including pyrimethamine plus sulfadiazine plus leucovorin **(AI),** and in consultation with appropriate specialists **(BIII).**[2,47-49] In general pyrimethamine should be avoided in the first trimester of pregnancy because of teratogenicity concerns, but in the case of TE, the benefit of using pyrimethamine to the mother outweighs the risk to the fetus. Of note, this regimen is often used in the treatment of fetuses with toxoplasmosis.[93] The preferred alternative regimen for pregnant patients with TE who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin **(AI).**[47,48] If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, TMP-SMX should be utilized in place of pyrimethamine-sulfadiazine or pyrimethamine-clindamycin **(BI).**

## *Prophylaxis During Pregnancy*

The indications for primary prophylaxis for TE during pregnancy, and the medications and dosages used, are the same as for nonpregnant individuals with HIV. TMP-SMX is the preferred therapy. The risks of TMP-SMX in the first trimester, as discussed for PCP, must be balanced against the risk of TE. Secondary prophylaxis should be provided, using the same indications as for nonpregnant people. Over the past several decades, dapsone (also used for primary prophylaxis) has been used safely in pregnancy to treat leprosy, malaria, and various dermatologic conditions.[108,109] Dapsone appears to cross the placenta.[108,110]

When providing preconception care for people of pregnancy potential with HIV and receiving TE prophylaxis, providers should discuss the option of deferring pregnancy until TE prophylaxis can be safely discontinued **(BIII).**

## *Pregnancy-Specific Medication Concerns*

Spiramycin is recommended to prevent transmission at <14 weeks gestation in the setting of acute primary infection during pregnancy or symptomatic reactivation of *T. gondii* **(AII).**[101,103,111] Spiramycin is not commercially available in the United States. Please see Preventing Congenital Infection: Initial Therapy and Surveillance on how to obtain spiramycin.

Pyrimethamine to prevent transmission should be avoided in the first trimester because of teratogenicity concerns with birth defects in animals, however it is recommended as first-line treatment for maternal TE **(BIII),** where the benefit of using pyrimethamine in a pregnant person outweighs the risk to the fetus. Additionally, pyrimethamine is often used in the setting of a positive fetal diagnosis.[112,113] Pyrimethamine can be administered to pregnant people after the first trimester since human data have not suggested an increased risk of birth defects.[89,114-117]

Sulfadiazine appears safe in pregnancy, without clear evidence of adverse fetal or neonatal outcome.[118,119] Although there are no studies published to date directly linking late third-trimester maternal sulfadiazine to neonatal death or kernicterus, the infant's care provider should be notified of maternal sulfa use in late pregnancy.

Clindamycin, suggested as part of an alternative regimen for patients with TE, is considered safe throughout pregnancy. Atovaquone, used both for prophylaxis and treatment of TE, may be used if indicated. While there are limited data on atovaquone safety in human pregnancy, preclinical studies

have not demonstrated maternal or fetal toxicity.[115] As noted above, dapsone has been used safely in pregnant persons for TE prophylaxis though with long-term therapy, there is a risk of mild hemolysis and a potential—although extremely low—risk of hemolytic anemia in exposed fetuses with glucose-6-phosphate dehydrogenase (or G6PD) deficiency.[108,120]

A detailed discussion of TMP-SMX and pregnancy is reviewed in the PCP chapter.

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