Toxoplasmosis

Updated: September 9, 2025
Reviewed: June 23, 2026

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 advanced HIV disease 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 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 First Episode of *Toxoplasma gondii* Encephalitis (Primary Prophylaxis)

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*

- (Atovaquone[b] 1,500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily **(CIII)**

Indication for Discontinuing Primary Prophylaxis

- CD4 count >200 cells/mm^3 for >3 months and sustained HIV RNA below limits of detection in response to ARV therapy **(AI);** *or*
- 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)**

Indication for Restarting Primary Prophylaxis

- CD4 count <100 cells/mm^3 **(AIII)**
- 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 all people with HIV.

[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 observation 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] Some clinicians would stop primary prophylaxis in people with HIV with CD4 counts of 100 cells/mm^3 to 200 cells/mm^3 if HIV plasma RNA levels remain below limits of detection for ≥3 months to 6 months; definitive data for a more precise recommendation are lacking **(BII).**[44]

Treating Disease

Recommendations for Treating Toxoplasmosis

Preferred Regimens for Acute Infection
• Pyrimethamine 200 mg PO once, followed by weight-based dosing **(AI):**
  ○ 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)
  ○ 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)
or
• TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) twice daily **(AII)**
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).**
Alternative Regimens for Acute Infection
• (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*
• Atovaquone[b] 1,500 mg PO twice daily + (pyrimethamine + leucovorin)[c] **(BII),** *or*
• Atovaquone[b] 1,500 mg PO twice daily + sulfadiazine[d] **(BII),** *or*
• Atovaquone[b] 1,500 mg PO twice daily **(BII)**
• For patients with a history of sulfa allergy, rapid sulfa desensitization may be attempted using one of several published strategies **(BI).**
• 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).**
Total Duration for Treating Acute Infection
• At least 6 weeks **(BII);** longer duration 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.

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* Encephalitis During Pregnancy

- Treatment regimen is the same as for all people with HIV **(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 woman 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 folic acid 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 intravenous 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 well understood; 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 radiographic 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 (Including IRIS)

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 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

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

During pregnancy, documentation of baseline *T. gondii* serologic status (IgG only) should be obtained 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 women with HIV with severe immunosuppression.[88-92] Knowing toxoplasmosis serostatus 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.[93,94]

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.[95,96] 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[96,97] (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 screening and treatment for *T. gondii* during pregnancy is universal, 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.[98] 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

During pregnancy, evidence of primary toxoplasmic infection without TE should be evaluated and managed 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.[99-105]

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 folic acid should be utilized in place of pyrimethamine-sulfadiazine **(BII).**[106,107]

In cases of suspect 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).**[96] In addition, patients should undergo an amniocentesis with PCR testing for *T. gondii* DNA in the amniotic fluid.[108] Amniocentesis does not appear to increase the risk of perinatal HIV transmission, particularly in people receiving ARV therapy.[109] Therefore, PCR of amniotic fluid can be considered during gestation in pregnant women on ARV therapy with serologic evidence of recently acquired *Toxoplasma* infection; women suspected to have reactivated their *Toxoplasma* latent infection during pregnancy; and those with ultrasound findings suggestive of fetal *T. gondii* infection **(BIII).**[96] In an effort to minimize false-negative results, amniotic fluid testing for *T. gondii* PCR should be avoided at less than 18-week gestation.[110]

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 folic acid **(AII).**

Pediatric-care providers should be informed about mothers 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*

During pregnancy, treatment of TE should be the same as in other adults with HIV **(BIII),** including pyrimethamine plus sulfadiazine plus leucovorin **(AIII),** 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.[96] The preferred alternative regimen for pregnant women with TE who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin **(AIII).**[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 **(BIII).**

Prophylaxis During Pregnancy

During pregnancy, the indications for primary prophylaxis for TE, and the medications and dosages used, are the same as for other persons 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 other people with HIV. 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.[111,112] Dapsone appears to cross the placenta.[111,113]

When providing preconception care for women of pregnancy potential with HIV who are 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).**[104,106,114] 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 woman outweighs the risk to the fetus. Additionally, pyrimethamine is often used in the setting of a positive fetal diagnosis.[115,116] Pyrimethamine can be administered after the first trimester since human data have not suggested an increased risk of birth defects.[117-121]

Sulfadiazine appears safe in pregnancy, without clear evidence of adverse fetal or neonatal outcome.[122,123] 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.[118] As noted above, dapsone has been used safely in pregnant women 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.[111,124]

A detailed discussion of TMP-SMX and pregnancy, including the use of folic acid, is reviewed in the PCP chapter.

References

1. Luft BJ, Conley F, Remington JS, et al. Outbreak of central-nervous-system toxoplasmosis in western Europe and North America. *Lancet*. 1983;1(8328):781-784. Available at: https://www.pubmed.ncbi.nlm.nih.gov/6132129.
2. Luft BJ, Hafner R, Korzun AH, et al. Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. Members of the ACTG 077p/ANRS 009 Study Team. *N Engl J Med*. 1993;329(14):995-1000. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8366923.
3. Wong B, Gold JW, Brown AE, et al. Central-nervous-system toxoplasmosis in homosexual men and parenteral drug abusers. *Ann Intern Med*. 1984;100(1):36-42. Available at: https://www.pubmed.ncbi.nlm.nih.gov/6691657.
4. Israelski DM, Chmiel JS, Poggensee L, Phair JP, Remington JS. Prevalence of *Toxoplasma* infection in a cohort of homosexual men at risk of AIDS and toxoplasmic encephalitis. *J Acquir Immune Defic Syndr*. 1993;6(4):414-418. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8455146.
5. Boyer KM, Holfels E, Roizen N, et al. Risk factors for *Toxoplasma gondii* infection in mothers of infants with congenital toxoplasmosis: implications for prenatal management and screening. *Am J Obstet Gynecol*. 2005;192(2):564-571. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15696004.
6. Siegel SE, Lunde MN, Gelderman AH, et al. Transmission of toxoplasmosis by leukocyte transfusion. *Blood*. 1971;37(4):388-394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4927414.
7. Gay J, Gendron N, Verney C, et al. Disseminated toxoplasmosis associated with hemophagocytic syndrome after kidney transplantation: a case report and review. *Transpl Infect Dis*. 2019;21(5):e13154. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31373746.
8. Ramanan P, Scherger S, Benamu E, et al. Toxoplasmosis in non-cardiac solid organ transplant recipients: a case series and review of literature. *Transpl Infect Dis*. 2020;22(1):e13218. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31769583.
9. Vanjak A, Canoui E, Honsel V, et al. Early primary toxoplasmosis transmitted by liver graft: a case report. *Infect Dis Now*. 2021;51(3):315-316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33934813.
10. Safarpour H, Cevik M, Zarean M, et al. Global status of *Toxoplasma gondii* infection and associated risk factors in people living with HIV. *AIDS*. 2020;34(3):469-474. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31714356.
11. Jones JL, Kruszon-Moran D, Elder S, et al. Toxoplasma gondii infection in the United States, 2011-2014. *Am J Trop Med Hyg*. 2018;98(2):551-557. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29260660.
12. McCall J, Rothfeldt L, Giesbrecht K, et al. Public health surveillance and reporting for human toxoplasmosis - six states, 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(28):889-893. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35834417.
13. Abgrall S, Rabaud C, Costagliola D, Clinical Epidemiology Group of the French Hospital Database on HIV. Incidence and risk factors for toxoplasmic encephalitis in human immunodeficiency virus-infected patients before and during the highly active

antiretroviral therapy era. *Clin Infect Dis*. 2001;33(10):1747-1755. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11595976.
14. Leport C, Chene G, Morlat P, et al. Pyrimethamine for primary prophylaxis of toxoplasmic encephalitis in patients with human immunodeficiency virus infection: a double-blind, randomized trial. ANRS 005-ACTG 154 Group Members. Agence Nationale de Recherche sur le SIDA. AIDS Clinical Trial Group. *J Infect Dis*. 1996;173(1):91-97. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8537688.
15. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS. Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. *JAMA*. 1984;252(7):913-917. Available at: https://www.pubmed.ncbi.nlm.nih.gov/6748191.
16. Gray F, Gherardi R, Wingate E, et al. Diffuse "encephalitic" cerebral toxoplasmosis in AIDS.Report of four cases. *J Neurol*. 1989;236(5):273-277. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2760644.
17. Kupfer MC, Zee CS, Colletti PM, Boswell WD, Rhodes R. MRI evaluation of AIDS-related encephalopathy: toxoplasmosis vs. lymphoma. *Magn Reson Imaging*. 1990;8(1):51-57. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2325518.
18. Pierce MA, Johnson MD, Maciunas RJ, et al. Evaluating contrast-enhancing brain lesions in patients with AIDS by using positron emission tomography. *Ann Intern Med*. 1995;123(8):594-598. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7677300.
19. Ruiz A, Ganz WI, Post MJ, et al. Use of thallium-201 brain SPECT to differentiate cerebral lymphoma from *Toxoplasma* encephalitis in AIDS patients. *AJNR Am J Neuroradiol*. 1994;15(10):1885-1894. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7863938.
20. Derouin F, Leport C, Pueyo S, et al. Predictive value of Toxoplasma gondii antibody titres on the occurrence of toxoplasmic encephalitis in HIV-infected patients. ANRS 005/ACTG 154 Trial Group. *AIDS*. 1996;10(13):1521-1527. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8931787.
21. Conley FK, Jenkins KA, Remington JS. *Toxoplasma gondii* infection of the central nervous system. Use of the peroxidase-antiperoxidase method to demonstrate *Toxoplasma* in formalin fixed, paraffin embedded tissue sections. *Hum Pathol*. 1981;12(8):690-698. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7026410.
22. Robert-Gangneux F, Darde ML. Epidemiology of and diagnostic strategies for toxoplasmosis. *Clin Microbiol Rev*. 2012;25(2):264-296. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22491772.
23. Novati R, Castagna A, Morsica G, et al. Polymerase chain reaction for *Toxoplasma gondii* DNA in the cerebrospinal fluid of AIDS patients with focal brain lesions. *AIDS*. 1994;8(12):1691-1694. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7888118.
24. Cinque P, Scarpellini P, Vago L, Linde A, Lazzarin A. Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. *AIDS*. 1997;11(1):1-17. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9110070.
25. Mesquita RT, Ziegler AP, Hiramoto RM, Vidal JE, Pereira-Chioccola VL. Real-time quantitative PCR in cerebral toxoplasmosis diagnosis of Brazilian human immunodeficiency virus-infected patients. *J Med Microbiol*. 2010;59(Pt 6):641-647. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20150319.

26. Ciricillo SF, Rosenblum ML. Use of CT and MR imaging to distinguish intracranial lesions and to define the need for biopsy in AIDS patients. *J Neurosurg*. 1990;73(5):720-724. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2213162.
27. Raffi F, Aboulker JP, Michelet C, et al. A prospective study of criteria for the diagnosis of toxoplasmic encephalitis in 186 AIDS patients. The BIOTOXO Study Group. *AIDS*. 1997;11(2):177-184. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9030364.
28. Antinori A, Ammassari A, De Luca A, et al. Diagnosis of AIDS-related focal brain lesions: a decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF. *Neurology*. 1997;48(3):687-694. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9065549.
29. Antinori A, De Rossi G, Ammassari A, et al. Value of combined approach with thallium-201 single-photon emission computed tomography and Epstein-Barr virus DNA polymerase chain reaction in CSF for the diagnosis of AIDS-related primary CNS lymphoma. *J Clin Oncol*. 1999;17(2):554-560. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10080599.
30. Corcoran C, Rebe K, van der Plas H, Myer L, Hardie DR. The predictive value of cerebrospinal fluid Epstein-Barr viral load as a marker of primary central nervous system lymphoma in HIV-infected persons. *J Clin Virol*. 2008;42(4):433-436. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18455472.
31. Koralnik IJ, Boden D, Mai VX, Lord CI, Letvin NL. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. *Neurology*. 1999;52(2):253-260. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9932940.
32. U.S. Department of Health and Human Services. FoodSafety.gov: your gateway to federal food safety information. Available at: https://www.foodsafety.gov Accessed: March 26
33. Carr A, Tindall B, Brew BJ, et al. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med*. 1992;117(2):106-111. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1351371.
34. Miro JM, Murray HW, Katlama C. Toxoplasmosis. R. Dolin, H. Masur and M. S. Saag, eds.In. AIDS Therapy Third.ed New York, New York. Churchill Livingstone 2008:659-681. Accessed: September 22, 2022.
35. Podzamczer D, Salazar A, Jimenez J, et al. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of Pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med*. 1995;122(10):755-761. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7717598.
36. Opravil M, Hirschel B, Lazzarin A, et al. Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 1995;20(3):531-541. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7756472.
37. Girard PM, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis in HIV infection. The PRIO Study Group. *N Engl J Med*. 1993;328(21):1514-1520. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8479488.

38. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. 1995;332(11):693-699. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7854375.
39. Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis*. 2000;182(2):611-615. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10915098.
40. Kirk O, Lundgren JD, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? *AIDS*. 1999;13(13):1647-1651. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10509565.
41. Furrer H, Opravil M, Bernasconi E, Telenti A, Egger M. Stopping primary prophylaxis in HIV-1-infected patients at high risk of toxoplasma encephalitis. Swiss HIV Cohort Study. *Lancet*. 2000;355(9222):2217-2218. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10881897.
42. Mussini C, Pezzotti P, Govoni A, et al. Discontinuation of primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study. *J Infect Dis*. 2000;181(5):1635-1642. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10823763.
43. Miro JM, Lopez JC, Podzamczer D, et al. Discontinuation of primary and secondary *Toxoplasma gondii* prophylaxis is safe in HIV-infected patients after immunological restoration with highly active antiretroviral therapy: results of an open, randomized, multicenter clinical trial. *Clin Infect Dis*. 2006;43(1):79-89. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16758422.
44. Miro J, Esteve A, Furrer H, Opportunistic Infection Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. Safety of stopping primary *T. gondii* prophylaxis with suppressed viremia and CD4>100. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA. Available at: https://www.croiconference.org/sessions/safety-stopping-primary-t-gondii-prophylaxis-suppressed-viremia-and-cd4100.
45. Opportunistic Infections Project Team of the Collaboration of Observational HIVERiE, Mocroft A, Reiss P, et al. Is it safe to discontinue primary *Pneumocystis jiroveci* pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/microL? *Clin Infect Dis*. 2010;51(5):611-619. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20645862.
46. Atkinson A, Miro JM, Mocroft A, et al. No need for secondary *Pneumocystis jirovecii* pneumonia prophylaxis in adult people living with HIV from Europe on ART with suppressed viraemia and a CD4 cell count greater than 100 cells/microL. *J Int AIDS Soc*. 2021;24(6):e25726. Available at: https://www.pubmed.ncbi.nlm.nih.gov/34118121.
47. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis*. 1996;22(2):268-275. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8838183.

48. Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. The California Collaborative Treatment Group. *Ann Intern Med*. 1992;116(1):33-43. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1727093.
49. Leport C, Raffi F, Matheron S, et al. Treatment of central nervous system toxoplasmosis with pyrimethamine/sulfadiazine combination in 35 patients with the acquired immunodeficiency syndrome. Efficacy of long-term continuous therapy. *Am J Med*. 1988;84(1):94-100. Available at: https://www.pubmed.ncbi.nlm.nih.gov/3337134.
50. Leport C, Meulemans A, Robine D, Dameron G, Vilde JL. Levels of pyrimethamine in serum and penetration into brain tissue in humans. *AIDS*. 1992;6(9):1040-1041. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1388895.
51. Van Delden C, Hirschel B. Folinic acid supplements to pyrimethamine-sulfadiazine for *Toxoplasma* encephalitis are associated with better outcome. *J Infect Dis*. 1996;173(5):1294-1295. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8627092.
52. Torre D, Casari S, Speranza F, et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Italian Collaborative Study Group. *Antimicrob Agents Chemother*. 1998;42(6):1346-1349. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9624473.
53. Pellegrino D, Gryschek R, de Oliveira ACP, Marcusso R, Correia A, Vidal JE. Efficacy and safety of trimethoprim-sulfamethoxazole in HIV-infected patients with cerebral toxoplasmosis in Brazil: a single-arm open-label clinical trial. *Int J STD AIDS*. 2019;30(12):1156-1162. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31558125.
54. Beraud G, Pierre-Francois S, Foltzer A, et al. Cotrimoxazole for treatment of cerebral toxoplasmosis: an observational cohort study during 1994–2006. *Am J Trop Med Hyg*. 2009;80(4):583-587. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19346380.
55. Prosty C, Hanula R, Levin Y, Bogoch, II, McDonald EG, Lee TC. Revisiting the evidence base for modern-day practice of the treatment of toxoplasmic encephalitis: a systematic review and meta-analysis. *Clin Infect Dis*. 2023;76(3):e1302-e1319. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35944134.
56. Girard PM, Lepretre A, Detruchis P, Matheron S, Coulaud JP. Failure of pyrimethamine-clindamycin combination for prophylaxis of *Pneumocystis carinii* pneumonia. *Lancet*. 1989;1(8652):1459. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2567474.
57. Solensky R. Drug desensitization. *Immunol Allergy Clin North Am*. 2004;24(3):425-443, vi. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15242719.
58. Gluckstein D, Ruskin J. Rapid oral desensitization to trimethoprim-sulfamethoxazole (TMP-SMZ): use in prophylaxis for *Pneumocystis carinii* pneumonia in patients with AIDS who were previously intolerant to TMP-SMZ. *Clin Infect Dis*. 1995;20(4):849-853. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7795084.
59. Nguyen MT, Weiss PJ, Wallace MR. Two-day oral desensitization to trimethoprim-sulfamethoxazole in HIV-infected patients. *AIDS*. 1995;9(6):573-575. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7662195.
60. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for *Pneumocystis carinii* pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse

reaction to TMP-SMZ. *J Infect Dis*. 2001;184(8):992-997. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11574913.
61. Demoly P, Messaad D, Sahla H, et al. Six-hour trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients. *J Allergy Clin Immunol*. 1998;102(6 Pt 1):1033-1036. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9847446.
62. Bonfanti P, Pusterla L, Parazzini F, et al. The effectiveness of desensitization versus rechallenge treatment in HIV-positive patients with previous hypersensitivity to TMP-SMX: a randomized multicentric study. C.I.S.A.I. Group. *Biomed Pharmacother*. 2000;54(1):45-49. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10721462.
63. Chirgwin K, Hafner R, Leport C, et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome: ACTG 237/ANRS 039 Study. AIDS Clinical Trials Group 237/Agence Nationale de Recherche sur le SIDA, Essai 039. *Clin Infect Dis*. 2002;34(9):1243-1250. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11941551.
64. Kovacs JA. Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. The NIAID-Clinical Center Intramural AIDS Program. *Lancet*. 1992;340(8820):637-638. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1355212.
65. Torres RA, Weinberg W, Stansell J, et al. Atovaquone for salvage treatment and suppression of toxoplasmic encephalitis in patients with AIDS. Atovaquone/Toxoplasmic Encephalitis Study Group. *Clin Infect Dis*. 1997;24(3):422-429. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9114194.
66. Katlama C, Mouthon B, Gourdon D, Lapierre D, Rousseau F. Atovaquone as long-term suppressive therapy for toxoplasmic encephalitis in patients with AIDS and multiple drug intolerance. Atovaquone Expanded Access Group. *AIDS*. 1996;10(10):1107-1112. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8874627.
67. Saba J, Morlat P, Raffi F, et al. Pyrimethamine plus azithromycin for treatment of acute toxoplasmic encephalitis in patients with AIDS. *Eur J Clin Microbiol Infect Dis*. 1993;12(11):853-856. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8112357.
68. Jacobson JM, Hafner R, Remington J, et al. Dose-escalation, phase I/II study of azithromycin and pyrimethamine for the treatment of toxoplasmic encephalitis in AIDS. *AIDS*. 2001;15(5):583-589. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11316995.
69. Fernandez-Martin J, Leport C, Morlat P, Meyohas MC, Chauvin JP, Vilde JL. Pyrimethamine-clarithromycin combination for therapy of acute *Toxoplasma* encephalitis in patients with AIDS. *Antimicrob Agents Chemother*. 1991;35(10):2049-2052. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1836943.
70. Dhiver C, Milandre C, Poizot-Martin I, Drogoul MP, Gastaut JL, Gastaut JA. 5-Fluoro-uracil-clindamycin for treatment of cerebral toxoplasmosis. *AIDS*. 1993;7(1):143-144. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8442914.
71. Derouin F, Piketty C, Chastang C, Chau F, Rouveix B, Pocidalo JJ. Anti-*Toxoplasma* effects of dapsone alone and combined with pyrimethamine. *Antimicrob Agents Chemother*. 1991;35(2):252-255. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2024957.
72. Lacassin F, Schaffo D, Perronne C, Longuet P, Leport C, Vilde JL. Clarithromycin-minocycline combination as salvage therapy for toxoplasmosis in patients infected with

human immunodeficiency virus. *Antimicrob Agents Chemother*. 1995;39(1):276-277. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7695324.
73. Hagberg L, Palmertz B, Lindberg J. Doxycycline and pyrimethamine for toxoplasmic encephalitis. *Scand J Infect Dis*. 1993;25(1):157-160. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8460343.
74. Coleman B, Smith BR, Kapoor R, et al. Persistence of human immunodeficiency virus-associated cerebral toxoplasmosis lesions in successfully treated patients receiving combination antiretroviral therapy. *Open Forum Infect Dis*. 2023;10(5):ofad208. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37213420.
75. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19440326.
76. Pfeffer G, Prout A, Hooge J, Maguire J. Biopsy-proven immune reconstitution syndrome in a patient with AIDS and cerebral toxoplasmosis. *Neurology*. 2009;73(4):321-322. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19636053.
77. Tremont-Lukats IW, Garciarena P, Juarbe R, El-Abassi RN. The immune inflammatory reconstitution syndrome and central nervous system toxoplasmosis. *Ann Intern Med*. 2009;150(9):656-657. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19414855.
78. Martin-Blondel G, Alvarez M, Delobel P, et al. Toxoplasmic encephalitis IRIS in HIV-infected patients: a case series and review of the literature. *J Neurol Neurosurg Psychiatry*. 2011;82(6):691-693. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20660912.
79. Cabral RF, Valle Bahia PR, Gasparetto EL, Chimelli L. Immune reconstitution inflammatory syndrome and cerebral toxoplasmosis. *AJNR Am J Neuroradiol*. 2010;31(7):E65-66. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20507930.
80. van Bilsen WPH, van den Berg C, Rijnders BJA, et al. Immune reconstitution inflammatory syndrome associated with toxoplasmic encephalitis in HIV-infected patients. *AIDS*. 2017;31(10):1415-1424. Available at: https://www.pubmed.ncbi.nlm.nih.gov/28375874.
81. Jordan MK, Burstein AH, Rock-Kress D, et al. Plasma pharmacokinetics of sulfadiazine administered twice daily versus four times daily are similar in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. 2004;48(2):635-637. Available at: https://www.pubmed.ncbi.nlm.nih.gov/14742225.
82. Podzamczer D, Miro JM, Ferrer E, et al. Thrice-weekly sulfadiazine-pyrimethamine for maintenance therapy of toxoplasmic encephalitis in HIV-infected patients. Spanish Toxoplasmosis Study Group. *Eur J Clin Microbiol Infect Dis*. 2000;19(2):89-95. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10746493.
83. Duval X, Pajot O, Le Moing V, et al. Maintenance therapy with cotrimoxazole for toxoplasmic encephalitis in the era of highly active antiretroviral therapy. *AIDS*. 2004;18(9):1342-1344. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15362670.
84. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. *N Engl J Med*. 1998;339(26):1889-1895. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9862944.

85. Soriano V, Dona C, Rodriguez-Rosado R, Barreiro P, Gonzalez-Lahoz J. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. 2000;14(4):383-386. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10770540.
86. Bertschy S, Opravil M, Cavassini M, et al. Discontinuation of maintenance therapy against toxoplasma encephalitis in AIDS patients with sustained response to anti-retroviral therapy. *Clin Microbiol Infect*. 2006;12(7):666-671. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16774564.
87. Miro JM. Stopping secondary TE prophylaxis in suppressed patients with CD4 100-200 is not safe. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, WA. Available at: https://www.croiconference.org/sessions/stopping-secondary-te-prophylaxis-suppressed-patients-cd4-100-200-not-safe.
88. Marty P, Bongain A, Rahal A, et al. Prenatal diagnosis of severe fetal toxoplasmosis as a result of toxoplasmic reactivation in an HIV-1 seropositive woman. *Prenat Diagn*. 1994;14(5):414-415. Available at: https://pubmed.ncbi.nlm.nih.gov/8084862.
89. Minkoff H, Remington JS, Holman S, Ramirez R, Goodwin S, Landesman S. Vertical transmission of toxoplasma by human immunodeficiency virus-infected women. *Am J Obstet Gynecol*. 1997;176(3):555-559. Available at: https://pubmed.ncbi.nlm.nih.gov/9077606.
90. Biedermann K, Flepp M, Fierz W, Joller-Jemelka H, Kleihues P. Pregnancy, immunosuppression and reactivation of latent toxoplasmosis. *J Perinat Med*. 1995;23(3):191-203. Available at: https://pubmed.ncbi.nlm.nih.gov/8568611.
91. Low incidence of congenital toxoplasmosis in children born to women infected with human immunodeficiency virus. European Collaborative Study and Research Network on Congenital Toxoplasmosis. *Eur J Obstet Gynecol Reprod Biol*. 1996;68(1-2):93-96. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8886688.
92. Campos FA, Andrade GM, Lanna Ade P, Lage BF, Assumpção MV, Pinto JA. Incidence of congenital toxoplasmosis among infants born to HIV-coinfected mothers: case series and literature review. *Braz J Infect Dis*. 2014;18(6):609-617. Available at: https://pubmed.ncbi.nlm.nih.gov/25017666.
93. Li XL, Wei HX, Zhang H, Peng HJ, Lindsay DS. A meta analysis on risks of adverse pregnancy outcomes in *Toxoplasma gondii* infection. *PLoS One*. 2014;9(5):e97775. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24830795.
94. Dunn D, Wallon M, Peyron F, Petersen E, Peckham C, Gilbert R. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. *Lancet*. 1999;353(9167):1829-1833. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10359407.
95. Montoya JG. Laboratory diagnosis of *Toxoplasma gondii* infection and toxoplasmosis. *J Infect Dis*. 2002;185 Suppl 1:S73-82. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11865443.
96. Montoya JG, Remington JS. Management of *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis*. 2008;47(4):554-566. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18624630.
97. Mitchell CD, Erlich SS, Mastrucci MT, Hutto SC, Parks WP, Scott GB. Congenital toxoplasmosis occurring in infants perinatally infected with human immunodeficiency

virus 1. *Pediatr Infect Dis J*. 1990;9(7):512-518. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2371084.
98. Peyron F, Mc Leod R, Ajzenberg D, et al. Congenital toxoplasmosis in France and the United States: one parasite, two diverging approaches. *PLoS Negl Trop Dis*. 2017;11(2):e0005222. Available at: https://www.pubmed.ncbi.nlm.nih.gov/28207736.
99. Cortina-Borja M, Tan HK, Wallon M, et al. Prenatal treatment for serious neurological sequelae of congenital toxoplasmosis: an observational prospective cohort study. *PLoS Med*. 2010;7(10). Available at: https://www.pubmed.ncbi.nlm.nih.gov/20967235.
100. Hotop A, Hlobil H, Gross U. Efficacy of rapid treatment initiation following primary *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis*. 2012;54(11):1545-1552. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22460980.
101. Kieffer F, Wallon M, Garcia P, Thulliez P, Peyron F, Franck J. Risk factors for retinochoroiditis during the first 2 years of life in infants with treated congenital toxoplasmosis. *Pediatr Infect Dis J*. 2008;27(1):27-32. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18162934.
102. Prusa AR, Kasper DC, Pollak A, Gleiss A, Waldhoer T, Hayde M. The Austrian Toxoplasmosis Register, 1992–2008. *Clin Infect Dis*. 2015;60(2):e4-e10. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25216688.
103. Syrocot Study Group, Thiebaut R, Leproust S, Chene G, Gilbert R. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. *Lancet*. 2007;369(9556):115-122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17223474.
104. Mandelbrot L, Kieffer F, Sitta R, et al. Prenatal therapy with pyrimethamine + sulfadiazine vs spiramycin to reduce placental transmission of toxoplasmosis: a multicenter, randomized trial. *Am J Obstet Gynecol*. 2018;219(4):386 e381-386 e389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29870736.
105. Dunay IR, Gajurel K, Dhakal R, Liesenfeld O, Montoya JG. Treatment of toxoplasmosis: historical perspective, animal models, and current clinical practice. *Clin Microbiol Rev*. 2018;31(4). Available at: https://www.ncbi.nlm.nih.gov/pubmed/30209035.
106. Valentini P, Buonsenso D, Barone G, et al. Spiramycin/cotrimoxazole versus pyrimethamine/sulfonamide and spiramycin alone for the treatment of toxoplasmosis in pregnancy. *J Perinatol*. 2015;35(2):90-94. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25211284.
107. Buonsenso D, Pata D, Turriziani Colonna A, et al. Spyramicine and trimethoprim-sulfamethoxazole combination to prevent mother-to-fetus transmission of *Toxoplasma gondii* infection in pregnant women: a 28-years single-center experience. *Pediatr Infect Dis J*. 2022;41(5):e223-e227. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35175992.
108. de Oliveira Azevedo CT, do Brasil PE, Guida L, Lopes Moreira ME. Performance of polymerase chain reaction analysis of the amniotic fluid of pregnant women for diagnosis of congenital toxoplasmosis: a systematic review and meta-analysis. *PLoS One*. 2016;11(4):e0149938. Available at: https://www.pubmed.ncbi.nlm.nih.gov/27055272.
109. Mandelbrot L, Jasseron C, Ekoukou D, et al. Amniocentesis and mother-to-child human immunodeficiency virus transmission in the Agence Nationale de Recherches sur le SIDA et les Hepatites Virales French Perinatal Cohort. *Am J Obstet Gynecol*.

2009;200(2):160 e161-169. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18986640.
110. Romand S, Wallon M, Franck J, Thulliez P, Peyron F, Dumon H. Prenatal diagnosis using polymerase chain reaction on amniotic fluid for congenital toxoplasmosis. *Obstet Gynecol*. 2001;97(2):296-300. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11165598.
111. Brabin BJ, Eggelte TA, Parise M, Verhoeff F. Dapsone therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Saf*. 2004;27(9):633-648. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15230645.
112. Newman RD, Parise ME, Slutsker L, Nahlen B, Steketee RW. Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for prevention programmes in Plasmodium falciparum-endemic sub-Saharan Africa. *Trop Med Int Health*. 2003;8(6):488-506. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12791054.
113. Zuidema J, Hilbers-Modderman ES, Merkus FW. Clinical pharmacokinetics of dapsone. *Clin Pharmacokinet*. 1986;11(4):299-315. Available at: https://www.pubmed.ncbi.nlm.nih.gov/3530584.
114. Schneider MO, Faschingbauer F, Kagan KO, et al. Toxoplasma gondii infection in pregnancy - recommendations of the Working Group on Obstetrics and Prenatal Medicine (AGG - Section on Maternal Disorders). *Geburtshilfe Frauenheilkd*. 2023;83(12):1431-1445. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38046526.
115. Remington JS MR, Thulliez P, Desmonts G. Toxoplasmosis. Remington JS, O'Klein J, Wilson C and Baker C, eds.In. Infectious diseases of the fetus and newborn infant 6th.ed Amsterdam. Elsevier. 2007:947. Accessed: May 10 ,2024. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675473.
116. Practice bulletin no. 151: cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy. *Obstet Gynecol*. 2015;125(6):1510-1525. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26000539.
117. Peters PJ, Thigpen MC, Parise ME, Newman RD. Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Saf*. 2007;30(6):481-501. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17536875.
118. Nosten F, McGready R, d'Alessandro U, et al. Antimalarial drugs in pregnancy: a review. *Curr Drug Saf*. 2006;1(1):1-15. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18690910.
119. Wong SY, Remington JS. Toxoplasmosis in pregnancy. *Clin Infect Dis*. 1994;18(6):853-861; quiz 862. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8086543.
120. Dunn CS, Beyer C, Kieny MP, et al. High viral load and CD4 lymphopenia in rhesus and cynomolgus macaques infected by a chimeric primate lentivirus constructed using the env, rev, tat, and vpu genes from HIV-1 Lai. *Virology*. 1996;223(2):351-361. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8806570.
121. Deen JL, von Seidlein L, Pinder M, Walraven GE, Greenwood BM. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. *Trans R Soc Trop Med Hyg*. 2001;95(4):424-428. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11579889.

122. Baskin CG, Law S, Wenger NK. Sulfadiazine rheumatic fever prophylaxis during pregnancy: does it increase the risk of kernicterus in the newborn? *Cardiology*. 1980;65(4):222-225. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7388849.
123. Yu PA, Tran EL, Parker CM, et al. Safety of antimicrobials during pregnancy: a systematic review of antimicrobials considered for treatment and postexposure prophylaxis of plague. *Clin Infect Dis*. 2020;70(70 Suppl 1):S37-S50. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32435799.
124. Thornton YS, Bowe ET. Neonatal hyperbilirubinemia after treatment of maternal leprosy. *South Med J*. 1989;82(5):668. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2717998.