BRITISH COLUMBIA
CENTRE *for* EXCELLENCE
in HIV/AIDS

THERAPEUTIC GUIDELINES FOR OPPORTUNISTIC INFECTIONS TOXOPLASMOSIS

INITIAL RELEASE: MAY 2009

LAST UPDATED: JANUARY 2024

Providence Health Care
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VERSION 05.01.2024

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Abbreviations: A/P aerosol pentamidine; ART, antiretroviral therapy; CI, confidence interval; CSF, cerebrospinal fluid; D-P, dapsone-pyrimethamine; DS, double strength; EBV, Epstein-Barr virus; FBL, focal brain lesion; HAART, highly active antiretroviral therapy; IRIS, immune reconstitution inflammatory syndrome; LDH, lactate dehydrogenase; PCP, Pneumocystis jiroveci pneumonia; P-C, pyrimethamine-clindamycin; PCNSL, primary central nervous system lymphoma; PCR, polymerase chain reaction; PET, positron emission tomography; PLWH, persons living with HIV; PML, progressive multifocal leukoencephalopathy; P-S, pyrimethamine-sulfadiazine; PYFU, person-years of follow-up; RCT, randomized controlled trial; RR, risk ratio (relative risk); SPECT, single-photon emission computed tomography; SS, single strength; TE, Toxoplasma encephalitis; TMP-SMX, trimethoprim-sulfamethoxazole.

TOXOPLASMOSIS

I) SITES OF DISEASE AND CLINICAL PRESENTATION

In the immunocompetent host, primary infection is typically asymptomatic or self-limited and chronic latent toxoplasmosis is asymptomatic. Severe disease occurs almost exclusively in the setting of congenital infection or T-cell related immunodeficiency[1]. Toxoplasma encephalitis (TE) is the most common presentation among immunocompromised persons living with HIV (PLWH); however occasional patients present with ocular[2], pulmonary[3] or disseminated disease[4,5,6]. The symptoms associated with TE often include headaches, fever, focal neurological deficits, cognitive impairment, or seizures; whereas those with extracerebral forms of disease may present with non-specific febrile illness, ocular, or respiratory symptoms.

II) PROPHYLAXIS

a) Screening and preventing exposure

Recommendations: PLWH should be tested for the presence of co-infection with *Toxoplasma gondii* (*T. gondii*) as indicated by the presence of *Toxoplasma* IgG antibody at the time of initial HIV diagnosis(BIII). PLWH, particularly those who are *Toxoplasma* IgG negative, should be counselled to: i) avoid consuming undercooked meat and shellfish, and unwashed fruits and vegetables; ii) wash hands carefully after handling soil, raw meat and shellfish; and iii) delegate others (HIV-negative and non-pregnant) to change cat litter boxes[7], but the cat does not need to be removed from the household[8].

b) Indications for prophylaxis

Recommendation for primary prophylaxis: PLWH having both positive *Toxoplasma* IgG serology and a CD4 count <100 cells/μL(AII).

Recommendation for secondary prophylaxis (preventing recurrence): Any PLWH with a previous diagnosis of disease due to toxoplasmosis(AI).

Discussion. Advanced HIV disease with CD4 lymphopenia (typically CD4 <100 cells/μL and almost always <200 cells/μL)[9,10] combined with positive serology for *T. gondii* IgG identifies those at particular risk of developing disease, which in the setting of HIV is usually re-activation of latent infection rather than primary infection[1]. For example, in one series of 115 PLWH with TE, the proportion of cases with a CD4 count <100 cells/μL and <200 cells/μL was 70% and 88%, respectively[9]. PLWH who have either latent or active infection due to *T. gondii* usually have a positive serologic response with detectable IgG but not IgM. An order for toxoplasmosis serology typically generates results for both IgG and IgM. Seroprevalence for *T. gondii* in North American adults has ranged from 10%-40%[1,11], but is higher in Latin America, Europe, and Africa. A study in British Columbia reported the seroprevalence to be 20.7% in the Fraser Valley in 1994[12].

c) Prophylactic Regimen Options

i) Recommended Primary Prophylaxis[7]:

- TMP-SMX (trimethoprim-sulfamethoxazole) 1 double-strength (DS) tablet daily (AII)

Alternative regimens (if intolerant to TMP-SMX 1 DS tablet daily):

- TMP-SMX 1 double strength (DS) tablet 3 days per week(BIII)

OR

- TMP-SMX 1 single-strength (SS) tablet daily(BIII)

OR

- Dapsone 50 mg daily plus [pyrimethamine 50 mg once weekly plus leucovorin (folinic acid) 25 mg once weekly][13](BI)

OR

- Atovaquone solution 1500 mg/day plus/minus [pyrimethamine 25 mg/day plus leucovorin 10 mg/day](CIII)

Discussion. Multiple randomized controlled trials (RCTs) have evaluated the efficacy of various dosing regimens of TMP-SMX, and dapsone-pyrimethamine for primary prophylaxis of both TE and *Pneumocystis jirovecii* pneumonia (PCP) in PLWH with CD4 below 200 cells/μL[14,15,16]. Two placebo-controlled RCTs studied pyrimethamine monotherapy for prophylaxis of TE[17,18]. Except for one study where the TE event rate was low in both arms[18], both TMP-SMX and dapsone-pyrimethamine regimens were shown to be efficacious for preventing TE compared to aerosol pentamidine or placebo. For example, in one study the cumulative rates of TE among *T. gondii* IgG-positive PLWH after 24 months of follow-up with TMP-SMX and dapsone-pyrimethamine prophylaxis were 4% and 7%, respectively[14]. In contrast, prior to the introduction of TE prophylaxis, among *T. gondii* IgG-positive PLWH enrolled in the Chicago Multicenter AIDS Cohort Study (MACS), the rate of development of TE was 38% within 2 years of follow-up[11]. Once-daily single and double dose TMP-SMX primary and secondary PCP prophylaxis regimens have also been effective in preventing TE[19,20].

In a meta-analysis of prophylaxis regimens against PCP and TE in PLWH, TMP-SMX was equivalent to dapsone-pyrimethamine (D-P) for prevention of TE; however, aerosol pentamidine (A/P) was not protective (TMP-SMX vs A/P risk ratio [RR]: 0.78, 95% confidence interval [CI]: 0.55 to 1.11, D-P vs A/P RR: 0.72, 95% CI: 0.54 to 0.97)[21]. In addition, a subgroup analysis demonstrated reduced mortality in patients whose CD4 counts were <100 cells/μL and who were receiving TMP-SMX compared to dapsone-pyrimethamine.

Similar efficacy was observed for lower versus higher dose regimens of TMP-SMX[21,22].

ii) Recommended Secondary Prophylaxis (Chronic Maintenance Therapy)[7]:

- Sulfadiazine 2000-4000 mg PO daily in 2-4 divided doses (available through Health Protection Branch, see *Induction Therapy* below) plus pyrimethamine

25-50 mg PO/day plus leucovorin 10-25 mg PO/day(AI).

Alternative regimens

- Clindamycin 600 mg PO every 8 hours plus pyrimethamine 25-50 mg PO/day plus leucovorin 10-25 mg PO/day[23](BI)

OR

- TMP-SMX 1 DS tab BID[24](BII)

OR

- TMP-SMX 1 DS tab once daily(BII)

OR

- Atovaquone 750-1500 mg PO BID plus [pyrimethamine 25 mg PO/day plus leucovorin 10 mg PO/day][25](BII)

Discussion. The recurrence rate for toxoplasma encephalitis is in excess of 50% following the acute phase of treatment in the absence of secondary prophylaxis[23,26,27]. A pharmacokinetic study demonstrated that the same total daily dose of sulfadiazine may be given in 2 divided doses rather than the traditional 4 doses[28], and was previously utilized in a clinical trial[29].

Chronic maintenance therapy with sulfadiazine plus pyrimethamine was more effective using a daily versus a twice weekly regimen with 12-month relapse rates of 6% and 30%, respectively[30]. A subsequent similar comparative study conducted around the time of the beginning of the highly active antiretroviral therapy (HAART) era (1994-1997) compared a daily versus a thrice-weekly regimen of sulfadiazine plus pyrimethamine. The cumulative relapse rates were 17% and 19%, respectively (p=0.91)[29]. The only factor associated with a lower incidence of relapse in that study was the use of antiretroviral therapy. Maintenance therapy regimens which employ less frequent than daily dosing are not recommended due to limited published experience.

There is less experience with the above-mentioned alternative therapies. In contrast to sulfadiazine-pyrimethamine, clindamycin-pyrimethamine is associated with a higher toxoplasmosis relapse rate (22% versus 11%)[23] and does not provide adequate PCP prophylaxis, requiring the addition of another prophylactic[31](BI). TMP-SMX appears to be an effective alternative maintenance therapy based upon a pilot study comparing TMP-SMX (TMP 5 mg/kg/day) with sulfadiazine-pyrimethamine, which included a 3-month follow-up relapse rate of 2.7% and 0, respectively[24]. A favourable outcome with TMP-SMX[1] DS tablet BID as maintenance therapy in TE was reported in an observational study of 17 patients followed for a median of 31 months with only a single relapse (6%) being identified[32]. Atovaquone has been well tolerated in TE maintenance therapy, but is expensive, less readily available than TMP-SMX, and associated with a 1-year relapse rate of 26%[25].

d) Discontinuing Toxoplasmosis Prophylaxis

- **Recommendation for discontinuing primary prophylaxis.** Prophylaxis may be discontinued for PLWH who experience antiretroviral therapy (ART)-induced immune reconstitution associated with an increase in the CD4 count to >200 cells/μL for at least 3 months(AI), or if the CD4 is between 100-200/μL and the HIV RNA remains below 400 copies/mL for at least 3-6 months[33].
- **Recommendation for discontinuing secondary prophylaxis.** This may be considered for PLWH who have no signs and symptoms of TE and have responded well to ART, with sustained increases in CD4 counts to >200 cells/μL for ≥6 months(BI). In this situation, the risk of relapse appears to be very low, although only a small number of such PLWH have been studied.

Discussion. The safety of discontinuing primary prophylaxis for TE in PLWH who have a sustained response to ART with a CD4 count remaining >200 cells/μL for at least 3 months has been demonstrated in RCTs[34,35] and observational studies[36,37,38]. One of these RCTs included 355 PLWH who discontinued and 353 who continued prophylaxis. After a median follow-up of 6 months, there were no cases of TE diagnosed in either group[34]. Similar findings were reported by Miro, et al., (2006)[35], with no cases of TE identified in 196 PWLH who were followed for a median of 25 months after stopping primary prophylaxis. Among 3 observational studies of primary TE prophylaxis discontinuation with sample sizes ranging from 37-2, 491, only a single case of TE was identified[36,37,38].

It was many years later that discontinuation of primary TE prophylaxis was convincingly demonstrated to be safe for ART responders with a CD4 count of 100-200 cells/μL and an HIV RNA of <400 copies/mL[33]. This observational study included 10 European HIV cohorts and reported very low TE incidence rates among such responders, rates which were not significantly different between those continuing versus those who had stopped prophylaxis, with 0.7 episodes per 1000 person-years of follow-up (PYFU) and 0.8 episodes per 1000 PYFU, respectively[33].

The discontinuation of secondary TE prophylaxis among PLWH who have responded to ART with an increase in CD4 count to >200 cells/μL has been evaluated in an RCT[35] and several observational studies[38,39,40,41]. Although this represents a limited published experience, among the 86 PLWH included in these 5 studies, there was only a single relapse of TE documented during a median follow-up of 18-30 months[41].

e) Restarting Toxoplasmosis Prophylaxis

- **Recommendation for restarting primary prophylaxis[7].** Prophylaxis should be restarted if the CD4 count falls to <100 cells/μL(AIII), or if the HIV RNA becomes detectable again (other than a transient "blip", defined as an HIV RNA between 40 and 500 copies/mL) in a patient with CD4 cells of 100-200/μL(AIII).
- **Recommendation for restarting secondary prophylaxis[7].** Prophylaxis should be restarted if the CD4 falls to <200 cells/μL[40](AIII). It is not safe to discontinue secondary toxoplasmosis prophylaxis if the CD4 count is 100-200 cells/μL, even if the HIV RNA remains below the limit of detection[42].

Discussion. In regard to the circumstances in which primary TE prophylaxis needs to be restarted, all *T. gondii* IgG seropositive PLWH whose CD4 counts fall below 100 cells/μL should restart. However, the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) study has provided reassurance that the risk of developing TE is very low and not influenced by the presence of prophylaxis when the CD4 count is between 100-200 cells/μL provided that there is virologic suppression (HIV RNA <400 copies/mL)(see *Discontinuing Prophylaxis*)[33].

In contrast, secondary TE prophylaxis (chronic maintenance therapy) should be restarted if the CD4 count falls below 200 cells/μL regardless of whether or not virologic suppression has been maintained. A further study from COHERE evaluated the incidence of TE relapse among 1,151 PLWH who had previously been diagnosed with TE and began ART after 1997[42]. Among those with CD4 of 100-200 cells/μL, HIV RNA <400 copies/mL, and off prophylaxis, the incidence of TE relapse was significantly higher (1.9 relapses per 100 PYFU [95% CI: 0.75 to 3.8]) than that observed among PLWH with CD4 >200 cells/μL (0.5 episodes per 100 PYFU [95% CI: 0.3 to 0.8]; p=0.002)[42].

III) DIAGNOSIS OF TOXOPLASMA ENCEPHALITIS (TE)

a) Presumptive, empiric, and definitive diagnoses

Presumptive diagnosis of AIDS-related TE is supported by the following criteria:

1. HIV-positive and immune deficiency (CD4 count <200 cells/μL)
2. *T. gondii* seropositive (IgG)
3. Compatible clinical presentation (usually including more than one of the following):
    - Headaches
    - Fever
    - Seizures
    - Focal neurologic deficit (e.g., hemiparesis, aphasia, ataxia)
    - Cognitive impairment (e.g., confusion, reduced level of consciousness, coma)
4. Evidence of one or more mass lesions on CT or MRI compatible with toxoplasmosis (often multiple ring-enhancing lesions with a predilection for the basal ganglia).

Empiric Diagnosis of TE requires that a PLWH with presumptive TE has a favourable response to empiric therapy (see below)[43].

Definitive Diagnosis of TE depends upon the demonstration of *T. gondii* in a clinical specimen (either histopathology on brain biopsy or detection of *T. gondii* DNA by spinal fluid PCR) of a PLWH with compatible clinical and radiologic findings, as for presumptive diagnosis outlined above.

b) Differential Diagnosis of focal brain lesion(s) (FBL) in PLWH with advanced disease (CD4 <200 cells/μL). The main differential diagnoses for North American PLWH are toxoplasmosis and primary central nervous system lymphoma (PCNSL)[1]. Although far less common in this setting, other etiologies which may present with similar clinical and imaging findings include bacterial brain abscess, cryptococcoma, aspergillosis, and tuberculoma. The absence of inflammatory features of the focal brain lesions on CT or MRI (e.g., contrast enhancement, mass effect, or edema) usually distinguishes progressive multifocal leukoencephalopathy (PML) from TE, except if associated with PML immune reconstitution inflammatory syndrome (IRIS)[44].

c) Role of various diagnostic tests.

- **Serology** in the peripheral blood is positive for *T. gondii* IgG (but usually negative for IgM) in the vast majority of patients with AIDS-related TE. For example, in one series, *T. gondii* IgG was detectable in 56 (97%) of 58 PLWH diagnosed with TE[45]. However, in another study, 17% of those presenting with AIDS-related TE had negative serology for *T. gondii* IgG by immunofluorescence[9].

- **Imaging**. None of the imaging modalities are entirely specific for TE and they do not reliably differentiate TE from PCNSL. MRI is more sensitive than CT for detection of TE lesions[46]. Other approaches to differentiate TE from PCNSL include the use of functional nuclear imaging modalities such as positron emission tomography (PET) CT scan[47] and thallium-201 single-photon emission computed tomography (SPECT) scan[48]. Brain lesions of TE are hypometabolic whereas those due to PCNSL are hypermetabolic on PET. Increased uptake of thallium-201 on brain SPECT scan is evidence supporting a diagnosis of CNS malignancy such as PCNSL. TE is typically not associated with increased uptake on brain SPECT scan; however, false positive uptake of thallium-201 has been observed in some patients with TE who were receiving ART, raising doubt about the utility of this imaging modality for focal HIV-related brain lesions in the HAART era[49]. A recent meta-analysis of SPECT and PET for the diagnosis of PCNSL in PLWH suggested higher sensitivity and specificity with PET; however, the published experience with PET is limited[50].

  In the absence of ART resulting in immune reconstitution inflammatory syndrome (IRIS), the focal brain lesions of PML on CT or MRI are typically not associated with inflammatory features such as contrast-enhancement, mass effect or edema[51]. Occasionally, patients with TE may present with a fulminant "diffuse encephalitic" form of the disease without any focal lesions detectable on CT or MRI imaging, making the diagnosis particularly difficult[52].

- **Polymerase chain reaction (PCR) and other cerebrospinal fluid (CSF) studies.** Lumbar puncture is often non-diagnostic and contraindicated, depending upon the imaging features of the focal brain lesion(s) identified. However, PCR for *T. gondii* in TE has variable sensitivity but high specificity and standardized commercial test kits are available[53]. For HIV-related TE, PCR for *T. gondii* has sensitivity of approximately 50-60% and specificity of 96-100%[54,55,56]. If it is considered safe to perform a lumbar puncture, then other CSF investigations for the evaluation of alternate possible diagnoses should be performed, including cell counts, glucose, and protein; bacterial, fungal and

mycobacterial cultures; cryptococcal antigen; smears for acid fast bacilli and gram stain; PCR for *T. gondii, M. tuberculosis*, and possibly for JC virus and Epstein-Barr Virus (EBV). CSF EBV PCR has been associated with mixed results in the diagnosis of PCNSL, including a substantial false positive rate and a positive predictive value of only 29% in one study[57].

- **Brain biopsy.** This is usually reserved for PLWH who do not respond to an empiric course of treatment for TE or whose clinical presentation is not compatible with a presumptive diagnosis of TE. A diagnosis of PCNSL is only reliably established by brain biopsy. A meta-analysis of the diagnostic accuracy and safety of stereotactic brain biopsy in PLWH included 19 cohort studies with 820 PLWH[58]. The diagnostic success rate of 92% was associated with morbidity (usually hemorrhage) in 5% and mortality in 0.7%. The biopsy findings changed management and resulted in clinical improvement in 60% and 34%, respectively. The most common brain biopsy final diagnoses were PCNSL (27%), PML (21%), TE (20%), and HIV encephalitis (4%)[58]. A meta-analysis of brain biopsy in PLWH which included both stereotactic and open biopsies showed no difference in diagnostic success, findings prompting a change in management, or complications between the 2 procedures[59]. The diagnostic success rate in this study was higher for lesions associated with contrast-enhancement, with an odds ratio of 2.54 (95% CI: 1.25 to 5.15; p<0.01).
- **Evaluation for extracerebral toxoplasmosis.** This may be relevant for occasional PLWH who have symptoms of ocular disease or disseminated disease with predominant pulmonary involvement. Pulmonary disease has a high mortality rate and mimics PCP with reticulonodular pulmonary infiltrates. Bronchoalveolar lavage samples may reveal *T. gondii* trophozoites[60] on Giemsa-stained smears. In addition, serum LDH levels may be extremely elevated to levels well above those typically associated with PCP[61], a finding also associated with HIV-related disseminated histoplasmosis[62].

d) **Diagnostic decision analysis** of focal brain lesions (FBL) in PLWH based on clinical findings, imaging, and PCR results. The probability of certain diagnoses for a FBL has been estimated using the following variables: the presence of mass effect on CT/MRI; *T. gondii* IgG serology; the use of toxoplasmosis prophylaxis; and CSF PCR results for *T. gondii*-DNA, JC virus-DNA, and EBV-DNA. For example, a prospective study included 136 consecutive PWLH with FBLs in whom a definitive diagnosis was established either by brain biopsy or clinical response to empiric therapy for toxoplasmosis[45]. The probability of the final diagnosis being TE among those with positive *Toxoplasma* IgG and imaging evidence of mass effect in the absence of toxoplasmosis prophylaxis was 0.87, but dropped to 0.59 if prophylaxis was being taken. In the same study, PLWH who had FBLs with mass effect but who were seronegative for *Toxoplasma* IgG were most likely to have a final diagnosis of PCNSL, with a probability of 0.74 which increased to 0.96 if CSF was positive for EBV-DNA PCR. Finally, PLWH whose FBLs did not demonstrate mass effect were most likely to have PML with a probability of 0.81, which increased to 0.99 if

the CSF JC virus PCR was positive[45].

Empiric therapy for TE has been recommended for all PLWH presenting with FBLs with mass effect who have a CD4 count of <200 cells/μL[54]. However, while continuing empiric TE therapy, those who are *T. gondii* IgG seronegative should be considered for early brain biopsy, particularly if the risk of death within the 14-21 days of empiric therapy exceeds 10% when the final diagnosis is not TE but possibly treatable[63].

e) **Management algorithm:** Focal brain lesions. A management algorithm is outlined in the Figure: *Management of Focal Brain Lesions in PLWH*.

MANAGEMENT OF FOCAL BRAIN LESIONS IN PLWH

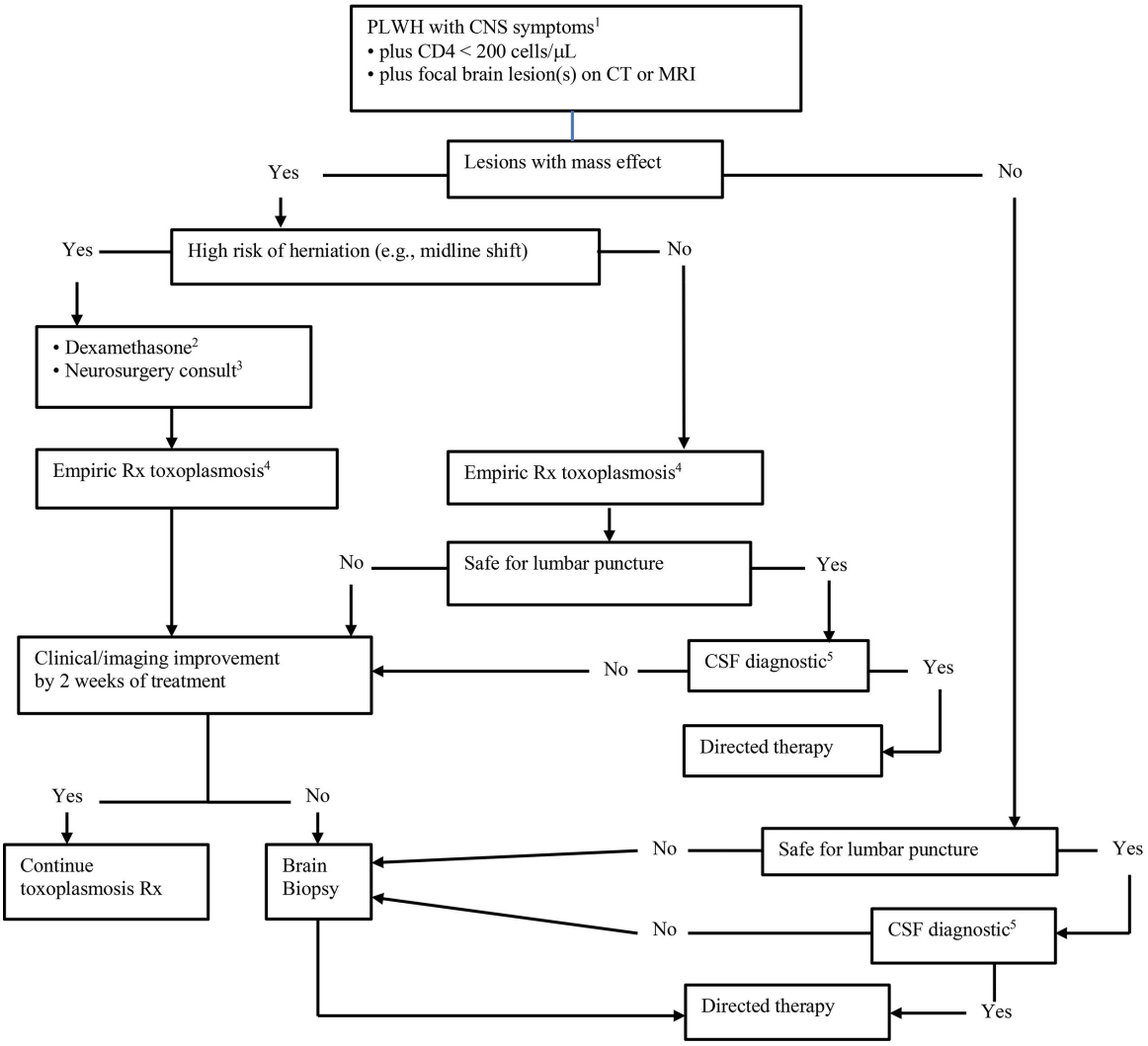

Figure legend

1. **CNS symptoms**. Central nervous system symptoms, e.g., headaches, cognitive impairment, focal neurologic deficit, seizures, fever.
2. **Dexamethasone**. 4 mg IV/PO q6h, followed by gradual taper over 2 weeks with clinical improvement.
3. **Neurosurgery consult**. Consideration of decompressive surgery including biopsy.
4. **Empiric Rx toxoplasmosis**. Empiric induction therapy (see text, IVb).
5. **CSF diagnostic**. CSF investigations may include cell counts, glucose, protein, cultures (bacterial, fungal, mycobacterial), smears for acid fast bacilli and gram stain, cryptococcal antigen, PCR for *T. gondii, M. tuberculosis*, JC virus, and Epstein-Barr virus (EBV).

IV) TREATMENT

a) Induction therapy

Indication for Empiric Therapy:
PLWH having one or more brain lesions which demonstrate mass effect in the setting of CD4 lymphopenia (CD4 <200 cells/μL) should be treated for TE[54].

Duration:
Treatment consists of induction therapy for 6 weeks, or possibly longer if there has been an incomplete response(BII). This is followed by maintenance therapy(AI) indefinitely or until the PLWH meets criteria for stopping maintenance therapy (see *Discontinuing Toxoplasmosis Prophylaxis* above).

Preferred regimen:

Sulfadiazine 1000 mg PO (<60 kg body weight) to 1500 mg PO (>60 kg body weight) q6h (currently only available as compassionate release through Health Protection Branch, phone 613-941-2108) plus pyrimethamine [200 mg PO loading dose, then 50 mg (<60 kg) to 75 mg PO (>60 kg)/day] plus leucovorin 10-25 mg PO/day[7](AI).

Alternative regimens:

- Clindamycin 600 mg IV or PO q6h plus pyrimethamine [200 mg PO loading dose, then 50 mg (<60 kg) to 75 mg PO (>60 kg)/day] plus leucovorin 10-25 mg PO/day[23,27](AI).

Other induction therapy options (expert advice should be sought before contemplating treatment with these agents)

- TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) IV or PO q12h[23](BI)

OR

- Atovaquone 1500 mg PO BID with meals plus pyrimethamine [200 mg PO loading dose, then 50mg (<60 kg) to 75 mg PO (>60 kg)/day] plus leucovorin 10-25 mg/day[64](BII).

OR

- Atovaquone 1500 mg PO BID with meals plus sulfadiazine 1000 mg PO (<60 kg body weight) to 1500 mg PO (>60 kg body weight) q6h[64](BII).

Discussion. Although some sources recommend limiting empiric TE therapy to those PLWH with FBLs whose CD4 counts are <100 cells/μL, there have been a significant number of PLWH with TE in the pre-HAART era whose CD4 counts at diagnosis have been between 100-200 cells/μL[9,10]; in addition, since the introduction of HAART, some PLWH may present with an unmasking immune reconstitution inflammatory syndrome (IRIS) TE presentation with higher CD4 than usual (see section V: *Toxoplasmosis IRIS and Timing of ART*). For these reasons, the inclusion of PLWH with FBLs and CD4 count <200 cells/ μL appears justified[54]. The main treatment options for HIV-related cerebral toxoplasmosis include combination pyrimethamine-sulfadiazine (P-S), pyrimethamine-clindamycin (P-C), or TMP-SMX; however, published

experience is more limited with TMP-SMX. Management guidelines in developed countries list P-S as the treatment of choice, with P-C as the favoured alternative based upon two RCTs[23,27] and a retrospective case series[65]. The largest RCT included 299 PLWH with TE randomized to receive P-S or P-C with similar favourable clinical responses (defined as complete or partial) reported in 76% and 68%, respectively (p=0.105, X2)[23]. However, PLWH who ended up discontinuing their assigned medication and crossing over from sulfadiazine to clindamycin usually did so due to drug side effects (mostly rashes), whereas crossovers from clindamycin to sulfadiazine were more often due to lack of response. No survival difference was noted between the two treatment regimens.

Potential advantages of TMP-SMX over pyrimethamine-based therapy for TE include greater access, lower cost, availability of an intravenous formulation, and prophylaxis for PCP (also provided by P-S, but not by P-C)[31,66]. One pilot RCT compared TMP (10 mg/kg body weight/day)-SMX (50 mg/kg/day) to P-S in 77 PLWH and demonstrated similar partial or complete response rates (83% with TMP-SMX and 85% with P-S), higher complete radiologic response rate with TMP-SMX (62% vs 39% with P-S), no difference in survival, but a lower rate of adverse drug reactions with TMP-SMX (12% vs 21% with P-S)[24]. Similarly, non-comparative observational studies including consecutive treated PLWH, a cohort study, and an open label single arm clinical trial also showed clinical response rates with TMP-SMX for HIV-related TE ranging from 75-85% and relatively low rates of adverse drug effects[67,68,69]. Given the above-mentioned potential advantages of TMP-SMX and the limited but favourable published experience in TE, it is usually the treatment of choice in resource-limited settings[54].

A recent systematic review and meta-analysis of these TE treatment regimens included 5 RCTs and 4 cohort studies[70]. Compared to P-S, treatment with P-C or TMP-SMX was associated with similar rates of partial or complete clinical response (P-C: RR: 0.87; 95% CI: 0.70 to 1.08; TMP-SMX: RR: 0.97; 95% CI: 0.78 to 1.21), radiologic response, skin rash, and drug discontinuation due to adverse events. However, liver dysfunction was more frequent with P-S than P-C (P-C vs P-S: RR: 0.48; 95% CI: 0.24 to 0.97). A systematic review of adverse drug effects for pyrimethamine-based treatment of toxoplasmosis identified bone marrow suppression, skin rash, gastrointestinal disturbance, and fever as the main complications[71].

The combination of atovaquone (oral suspension rather than the less well-absorbed earlier tablet formulation) with either pyrimethamine or sulfadiazine appears to have synergistic activity against *T. gondii* in an animal model and was associated with an induction therapy clinical response rate of 77% in 39 PLWH with TE[64]. Although comparative studies are not available, less favourable results have been observed with atovaquone monotherapy for induction or maintenance therapy[25,72]. Limited published experience suggests a possible role for other alternative regimens including either a macrolide (azithromycin or clarithromycin) or doxycycline in combination with pyrimethamine[73,74,75,76].

b) **Evaluating response to empiric therapy.** An MRI should be repeated after 2 weeks of treatment or earlier if there is no clinical response. Patients worsening by day 7 or not responding clinically by day 10-14 of a trial of empiric therapy should be considered for stereotactic brain biopsy[43](BII). A favourable clinical and radiologic response to empiric treatment confirms the diagnosis and warrants indefinite maintenance therapy. The

absence of a response warrants additional investigation. Empiric therapy for toxoplasmosis should not be discontinued on the basis of negative serum toxoplasma serology[9], somewhat atypical imaging findings, or a slow/delayed response. Empiric therapy should be continued until an alternate diagnosis has been established (e.g., by stereotactic brain biopsy). Negative serology for *T. gondii* (IgG antibodies) argues against the diagnosis TE, but does not exclude it.

c) Role of corticosteroids

Recommended use of corticosteroids: Corticosteroids (e.g., dexamethasone 4 mg every 6 hours initially, then tapered) should be reserved for PLWH with evidence of life-threatening mass effect and/or cerebral edema (e.g., evidence of midline shift on CT or MRI scan) during a trial of empiric therapy for CNS toxoplasmosis(BIII).

Discussion. The efficacy of adjunctive corticosteroids in TE has not been demonstrated in observational studies[77] which tend to be confounded by the tendency for corticosteroids to be administered to the most severely ill patients; and no RCT has been published. The disadvantages to the use of corticosteroids in this setting include the usual potential adverse effects, but in addition the confounding effect on the evaluation of the response to toxoplasmosis therapy, since corticosteroids are also associated with clinical improvement of PCNSL. Also, if the patient proceeds to brain biopsy, the diagnostic yield for PCNSL on histopathology may be reduced by corticosteroid use[78].

d) Maintenance therapy (see *Secondary Prophylaxis* above)

e) Adverse drug effects and monitoring

- **Pyrimethamine:** leukopenia, thrombocytopenia, megaloblastic anemia, hypersensitivity, gastrointestinal distress, and headaches. Cytopenias are mostly preventable by the addition of leucovorin, which is expensive and may not be necessary for all patients. Leucovorin dose adjustment (ranging from 10, 25, or 50 mg 4 times daily as needed) should be made according to the results of monitoring blood counts (e.g. neutrophils, platelets)(CIII).
- **Sulfadiazine:** cutaneous hypersensitivity, fever, leukopenia, crystalluria with renal impairment, nausea, vomiting, diarrhea, hepatotoxicity, and headache; less frequently, serum sickness, and rarely Stevens-Johnson syndrome. Adequate hydration reduces renal toxicity.
- **Clindamycin:** rash, gastrointestinal intolerance, hepatotoxicity, fever, and *C. difficile* colitis.
- **Monitoring:** laboratory studies include complete blood counts and differential, blood urea nitrogen (BUN), creatinine, bilirubin, alkaline phosphatase and alanine aminotransferase.

  The frequency of repeating these tests during the 6 weeks of induction therapy is 2-3 times per week; then during maintenance 1-2 times per month when counts are stable.

f) Pregnancy

Baseline *T. gondii* serology (IgG) should be obtained in all PLWH who are pregnant. The diagnosis and management of primary versus chronic *T. gondii* infection in pregnancy is beyond the scope of this document. The management of TE in pregnancy is much the same as for other patients regarding investigations and treatment, but should involve a specialist in maternal-fetal medicine. The treatment of choice is pyrimethamine/leucovorin plus sulfadiazine; however, pyrimethamine is potentially teratogenic and should not be used during the first trimester[7,79]. Sulfadiazine is safe in pregnancy despite some previous concerns regarding neonatal kernicterus associated with maternal sulfa drug use near the time of delivery[80]. In regard to alternative regimens, clindamycin is safe in pregnancy. Experience with atovaquone in pregnancy is limited; however it does not appear to be associated with fetal toxicity[81]. Prophylaxis for TE in pregnancy can be provided with TMP-SMX, and the risk of TMP-SMX during the first trimester needs to be weighed against the risk of TE[7]. Dapsone crosses the placenta but has also proven to be safe in pregnancy[82], despite the very low risk of hemolytic anemia should the fetus be glucose-6-phosphate dehydrogenase (G6PD)-deficient.

V) TOXOPLASMOSIS IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) AND TIMING OF ART

Toxoplasmosis encephalitis (TE) IRIS has rarely been reported. Both an unmasking type of IRIS (defined as TE developing after the initiation of ART)[83], and a paradoxical IRIS (defined as pre-existing TE worsening after ART initiation) have been reported[84]. In a series of 9 PLWH, unmasking TE-IRIS developed a median of 48.5 days after starting ART. In contrast to TE, TE-IRIS was associated with a higher median CD4 count of 222 cells/μL, and 2 PLWH who underwent brain biopsy had intense angiocentric CD8 lymphocyte predominant inflammatory infiltrates[83]. Three of 4 reported cases of paradoxical IRIS were associated with early initiation of ART within 1 week of starting anti-toxoplasma therapy, suggesting that ART should be delayed until at least 2 weeks of therapy is completed[84]. However, in a Dutch multicentre cohort study, there was no difference in the timing of ART initiation between those with and without paradoxical TE-IRIS, suggesting that it is probably safe to initiate ART 2-3 weeks after starting TE induction therapy[85]. In the same study, among 143 PLWH diagnosed with TE and at risk of paradoxical TE-IRIS there were 5 (3.5%) cases identified; and among 2,228 PLWH who started ART with a CD4<200 cells/μL and receiving primary prophylaxis, there were 8 cases diagnosed with unmasking TE-IRIS (0.36%). Although there are a lack of definitive data upon which to base a recommendation for the timing of initiation of ART in TE, it has been suggested that a 2-3 week delay after starting anti-toxoplasma therapy may be reasonable until further studies are available[7,86](CIII). Published experience with corticosteroids in managing TE-IRIS is scant, although corticosteroids have been recommended as for other opportunistic infection IRIS manifestations[87]. In severe TE-IRIS with impending herniation, high dose intravenous corticosteroid (e.g. methylprednisolone 1 gram IV daily) is recommended for 3-5 days, followed by a tapering course over 2-3 weeks[87]. Temporary discontinuation of ART is also a consideration in life-threatening TE-IRIS, however published clinical data to inform such management decisions are lacking.

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