Tuberculosis of the Central Nervous System in Immunocompromised Patients: HIV Infection and Solid Organ Transplant Recipients

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Central nervous system (CNS) tuberculosis (TB) is a devastating infection with high rates of morbidity and mortality worldwide and may manifest as meningitis, tuberculoma, abscess, or other forms of disease. Immunosuppression, due to either human immunodeficiency virus infection or solid organ transplantation, increases susceptibility for acquiring or reactivating TB and complicates the management of underlying immunosuppression and CNS TB infection. This article reviews how immunosuppression alters the clinical presentation, diagnosis, treatment, and outcome of TB infections of the CNS.

In ~1% of individuals with *Mycobacterium tuberculosis* infection, central nervous system (CNS) involvement develops, including meningitis, tuberculoma, abscess, or other manifestations [1]. Infection of the CNS is the most severe extrapulmonary manifestation of tuberculosis (TB), with a high mortality rate and residual neurologic sequelae, even with adequate treatment [2].

TB is one of the most important opportunistic infections in both patients with human immunodeficiency virus (HIV) infection and transplant recipients. Both patient populations have a high relative risk of disseminated TB (Table 1) and receive medications that complicate treatment. In addition, in both populations immune reconstitution inflammatory syndrome (IRIS) can develop [8, 9].

HIV infection significantly increases the risk for acquisition of TB, the rate of progression from latent to active disease, and TB-associated morbidity and mortality [5, 10, 11]. Extrapulmonary manifestations appear in ~40% of HIV-infected patients with TB [10]. Compared with HIV-negative individuals, HIV-positive individuals with TB are 5 times more likely to have CNS involvement [5].

Patients with immunosuppression following solid organ transplant (SOT) are also at increased risk for acquiring TB and presenting with extrapulmonary TB. Compared with the general population, SOT recipients are 20–74 times more likely to acquire TB [11, 12]. Most TB infections in transplant recipients are due to reactivation of dormant disease, although nosocomial infection and donor transmission have been reported [13].

This article reviews the clinical manifestations, diagnosis, and treatment of CNS TB in patients with immunodeficiency due to HIV infection or SOT. Bone marrow transplant patients are not included in this review because they have a lower risk of acquiring TB after transplantation and there is little published information on this patient population.

**MENINGITIS**

TB meningitis accounts for 5% of all extrapulmonary TB and is one of the most devastating manifestations of TB infection [14]. It occurs more frequently in children, particularly those <1 year of age [15, 16]. Of
Table 1. Relative Risk of Tuberculosis (TB) and Central Nervous System TB in Patients With HIV Infection and Solid Organ Transplant Recipients

<table>
<thead>
<tr>
<th>Patient category</th>
<th>TB</th>
<th>CNS TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected patients</td>
<td>20.6–36.7 [3]</td>
<td>2.1 [4], 5.0 [5], 5.3 [6]</td>
</tr>
<tr>
<td>SOT recipients [7]</td>
<td>( \ldots )</td>
<td>( \ldots )</td>
</tr>
<tr>
<td>Lung</td>
<td>73.3 ( \ldots ) ( \ldots ) ( \ldots )</td>
<td></td>
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<tr>
<td>Liver</td>
<td>29.5 ( \ldots ) ( \ldots ) ( \ldots )</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>19.0 ( \ldots ) ( \ldots ) ( \ldots )</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>13.7 ( \ldots ) ( \ldots ) ( \ldots )</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus; SOT, solid organ transplant; TB, tuberculosis.

a TB meningitis only.
b Limited or no data available.

adults with TB meningitis, 40%–66% have extrameningeal TB at the time of diagnosis [2, 17, 18].

The most common symptoms of TB meningitis include fever, headache, vomiting, and altered level of consciousness. Children are more likely to present with seizures, nausea, and vomiting; headache is less frequent [2]. The basilar meninges and cistern are frequently affected and cause cranial nerve dysfunction, especially of the sixth (abducens) and seventh (facial) cranial nerves [16, 19]. TB meningitis may have an insidious onset, so physicians should have a high clinical suspicion in young children with altered level of consciousness in TB-endemic areas.

Hydrocephalus is common during TB meningitis owing to high protein levels causing obstruction of cerebrospinal fluid (CSF) flow [20]. Intracranial vasculopathy is also frequent in TB meningitis, and stroke can occur as a complication of vasospasm, thrombosis, vasculitis, or hemorrhagic infarction [21].

In HIV-infected patients, TB is more likely to produce meningitis [22]. In a study of 2205 patients with TB, 10% of HIV-positive patients had TB meningitis compared with only 2% of patients without HIV infection [5]. The risk of TB meningitis is greater in HIV-infected patients with CD4 counts <100 cells/μL [23–25]. Although the clinical presentation of TB meningitis is generally similar irrespective of HIV status [5, 26–29], some studies have reported more frequent altered level of consciousness, lymph node involvement, and extrameningeal TB in HIV-infected people [5, 17, 26, 30]. One study reported that only 15% of HIV-infected patients with TB meningitis presented with the classic triad of fever, headache, and meningeal signs [23].

After SOT, the median time to development of posttransplant TB is 183 days, and CNS TB infections seem to have a similar temporal pattern [7]. The majority of patients present with disseminated infection, which is more frequent after liver and renal transplantation. Treatment with muromonab-CD3 (OKT3) or anti–T-cell antibodies significantly increases the risk of disseminated TB, whereas cyclosporine, tacrolimus, and azathioprine do not [11].

**TUBERCULOMA (TUBERCULOUS GRANULOMA)**

The clinical presentation of CNS tuberculosis is usually more subtle than that of TB meningitis and may include headache, seizures, focal neurologic deficits, and papilledema [31]. Tuberculomas accompany TB meningitis in 10% of patients and are multiple in a third of patients [32]. Lesions may occur in the brain, spinal cord, subarachnoid, subdural, or epidural space; they may be solitary but are most often multiple and accompanied by surrounding edema and ring enhancement [33]. In children, lesions tend to be infratentorial, whereas in adults they are typically supratentorial [34].

Clinical presentation of tuberculoma may differ in HIV-infected individuals. A small study in Spain included 4 HIV-infected individuals with tuberculoma who, in contrast to HIV-uninfected patients, all presented with fever and headache and none with seizures [35].

CNS tuberculoma after SOT may present up to 11 years following transplantation [36, 37]. Although immunosuppression and comorbidities probably complicate the presentation of posttransplantation CNS tuberculosis, too few cases have been reported to allow comment on potential differences in clinical presentation.

**TUBERCULOUS ABSCESS**

Tuberculous abscesses tend to be larger than tuberculomas, often >3 cm in diameter. The clinical presentation of tuberculous abscess is typically more acute than tuberculosis and includes fever, headache, and focal neurologic deficits [31].

In HIV-infected people, TB abscesses may occur more frequently; 1 study found that 20% of HIV-infected persons with CNS TB had tuberculous abscess [39], compared with 4%–7.5% of HIV-negative patients with CNS TB [40]. It is not known whether this increased frequency is a true effect or due to referral bias. HIV-induced suppression of cell-mediated immunity may inhibit the intracerebral response to TB bacilli, thus increasing the likelihood of abscess versus granuloma formation [39]. A review of 12 HIV-positive patients with tuberculous abscess reported that seizures, headache, altered level of consciousness, and hemiparesis were prominent presenting symptoms; all but 1 patient had solitary lesions [40].

In SOT patients, abscess also seems to be a common manifestation of CNS TB. In a review of TB after SOT, Singh et al reported that TB abscess was present in 5 of 18 patients (28%) with CNS TB [11].
### Table 2. Cerebrospinal Fluid Abnormalities in Patients With Central Nervous System Tuberculosis

<table>
<thead>
<tr>
<th>CSF finding</th>
<th>TB meningitis</th>
<th>Tuberculoma&lt;sup&gt;a&lt;/sup&gt;</th>
<th>TB and HIV infection&lt;sup&gt;b&lt;/sup&gt;</th>
<th>TB-associated IRIS</th>
</tr>
</thead>
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<tr>
<td><strong>Cytochemical profile (%) with finding</strong></td>
<td><strong>WBC count</strong>, 100–399 cells/µL [48]; lymphocyte predominance (85%) [18]; protein &gt;40 mg/dL (77%) [13]; CSF–serum glucose ratio &lt;0.6 (67%) [18]; opening pressure &gt;200 mm H&lt;sub&gt;2&lt;/sub&gt;O (54%) [18]</td>
<td>WBC counts normal or slightly to moderately elevated [49–51]; elevated protein (88%) [52]; low glucose (83%) [53]</td>
<td>Lower opening pressure [26]; CSF pleocytosis (CSF WBC count, ≥5 cells/µL) absent in 11%–18%; in patients with pleocytosis, WBC counts similar to those in patients without HIV infection [5, 23, 53]; others report lower CSF WBC counts [26, 27]; in patients with CD4 counts &lt;50 cells/µL, pleocytosis is less common (77% vs 85.2%), and median CSF cell counts lower (89 vs 246 cells/µL) [54, 55]; no significant difference in protein or glucose levels [56]; others report lower protein [27, 55]; 64% have classic triad of elevated protein, low glucose, and pleocytosis [23]</td>
<td>In series of 13 patients, CSF pleocytosis was absent in 2 (15%) [57]; in patients with pleocytosis, WBC counts are typically lower (median, 30 cells/µL; range, 14–65) [57]; median protein, 160 mg/mL, and glucose, 37.8 mmol/dL [57]</td>
</tr>
<tr>
<td><strong>Acid-fast bacilli stain</strong></td>
<td>20% positive in 1 series [18]; sensitivity, 37% with 1 CSF examination, 87% with 3 examinations [48]&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Typically negative [58]&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Similar sensitivity for HIV-infected patients, but higher mortality in those with positive smear sample [59]</td>
<td>Smear sample positive in 1 (9%) of 11 cases of meningitis [57]; negative in all 4 patients with tuberculoma [57]</td>
</tr>
<tr>
<td><strong>Acid-fast bacilli culture</strong></td>
<td>11% positive in 1 series [18]; sensitivity, 52% with 1 CSF examination, 83% with 3 examinations [48]&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Typically negative [58]&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Similar sensitivity for HIV-infected patients [60]; <em>Mycobacterium tuberculosis</em> more likely to be isolated from CSF [26, 56]</td>
<td>Smear sample positive in 1 (9%) of 11 patients with meningitis [57]; negative in all 4 patients with tuberculoma [57]</td>
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<td><strong>PCR findings</strong></td>
<td>Sensitivity, 4%–100%, depending on diagnostic criteria used and prior administration of antituberculosis therapy [2]; specificity, usually 100% (range, 38%–100%) [2]; diagnosis cannot be excluded based on negative PCR result</td>
<td>PCR may increase diagnostic yield [61, 62], but CSF findings are rarely positive</td>
<td>Similar findings in HIV-infected patients</td>
<td>Insufficient data</td>
</tr>
<tr>
<td><strong>IFN-γ levels</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CSF IFN-γ, &gt;6.4 IU/mL: sensitivity, 70%, and specificity, 94% [63]; simultaneous use of CSF PCR and IFN-γ increases sensitivity to 80% and specificity to 92.6% [63]</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
<td>Insufficient data</td>
</tr>
<tr>
<td><strong>ADA levels</strong></td>
<td>&gt;8 U/L: sensitivity, 59%; specificity, 96%, cannot discriminate between TB and bacterial meningitis [64]</td>
<td>Insufficient data</td>
<td>No difference in mean levels: 12.6 IU/L in HIV-infected patients vs 13.5 IU/L in patients without HIV infection [65]</td>
<td>Insufficient data</td>
</tr>
</tbody>
</table>

Abbreviations: ADA, adenosine deaminase; CNS, central nervous system; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IFN, interferon; IRIS, immune reconstitution inflammatory syndrome; PCR, polymerase chain reaction; TB, tuberculosis; WBC, white blood cell.

<sup>a</sup> Of patients with tuberculoma, 50% have concurrent TB meningitis [52].

<sup>b</sup> CSF lactic acid is elevated in HIV-infected patients with TB meningitis and can be useful for distinguishing TB meningitis from chronic HIV meningitis [65].

<sup>c</sup> When possible, a large volume of CSF (10 mL) should be obtained to increase the diagnostic yield of acid-fast bacilli stain and culture [66].

<sup>d</sup> Aspirate fluid may also be tested for presence of acid-fast bacilli. Tuberculoma fluid aspirates do not typically harbor bacilli, whereas abscess fluid is filled with organisms [41, 58].

<sup>a</sup> Note that these results are from a single study.
Miliary CNS TB, TB radiculomyelitis, and TB encephalitis are not reviewed, because there is little published information regarding these forms of CNS TB in HIV-infected patients or transplant recipients.

**DIAGNOSIS**

Diagnosis of TB outside the CNS can be useful for making a presumptive diagnosis of CNS TB. Ancillary diagnostic tests include chest radiography, tuberculin skin test, and sputum test. Abnormal chest radiographic findings are present in 41%–60% of patients with TB meningitis [41, 42], 17%–45% have a positive purified protein derivative test (positivity increases to 75% with 100-unit dose) [41, 42], and 50% have a positive sputum result [43]. An elevated level of serum interferon (IFN)–γ has high specificity for diagnosing TB and less interreader variability, and it is not affected by prior BCG vaccination [44]. HIV-infected patients with latent TB have variable results with one type of serum IFN-γ test (Quantiferon), and lower sensitivity is associated with higher degrees of immunodeficiency [45]. Given the similarity of the clinical presentation of CNS TB to other neurologic opportunistic infections, especially cryptococcal meningitis and cerebral toxoplasmosis, a high index of suspicion should be maintained for other opportunistic infections.

Thwaites et al and Törökk et al have developed and validated diagnostic algorithms for TB meningitis that use basic clinical and laboratory data [46, 47]. CSF culture remains the reference standard for diagnosing CNS TB; ancillary assays such as polymerase chain reaction (PCR), although specific, have widely variable sensitivity and should not be used to exclude the diagnosis of CNS TB (Table 2). Findings of small studies suggest that IFN-γ testing in CSF is both highly sensitive and specific for TB meningitis [63]. Compared with that in immunocompetent patients, the CSF profile in HIV-infected patients with TB meningitis has a wider range of findings [23]. Compared with patients with CD4 counts >50 cells/μL, patients with lower counts are less likely to have CSF pleocytosis or depressed glucose levels [54]. Table 3 summarizes the differences in presentation, diagnosis, neuroimaging findings, and outcome of CNS TB in HIV-infected patients compared with immunocompetent patients.

**TREATMENT**

**Immunocompetent Patients**

Given the low sensitivity of existing CSF tests for detecting TB and the slow growth of *M. tuberculosis* in culture, antituberculous treatment is often initiated empirically. Treatment is more complex for multidrug-resistant TB (MDR TB; resistant to isoniazid [INH] and rifampicin) and extensively drug-resistant TB (resistant to INH, rifampin, fluoroquinolones, capreomycin, kanamycin, and amikacin). In a study of 1614 patients with positive CSF cultures, the presence of isoniazid resistance was associated with 2.1 times higher risk of death [71]. Determining the prevalence of drug resistance is extremely important for guiding initial therapy, especially when sensitivities are pending or not feasible [72].

Monitoring TB medication levels in blood or CSF is rarely necessary except in patients with treatment failure, known malabsorptive states, or those who are receiving cycloserine and develop adverse CNS effects. Intrathecal treatment is not the standard of care, but successful use of intrathecal levofloxacin and amikacin for MDR TB has been reported [73].

The use of corticosteroids is widely accepted as adjuvant therapy for CNS TB, particularly for TB meningitis, as well as for CNS TB-associated IRIS (see below) [66]. A meta-analysis of 7 randomized controlled trials concluded that “corticosteroids should be used routinely in HIV-negative people...
<table>
<thead>
<tr>
<th>TB drug</th>
<th>Interactions with drugs for HIV infection</th>
<th>Interactions with drugs for transplant recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>No known interactions with NRTIs, NNRTIs, or PIs</td>
<td>May decrease metabolism of cyclosporine, tacrolimus, and sirolimus through CYP3A4 inhibition; may reduce corticosteroid levels and vice versa [11, 80]; no known interactions with MMF or azathioprine</td>
</tr>
<tr>
<td>Rifamycins: rifampicin and rifabutin</td>
<td>Rifampicin decreases concentrations of PIs and NNRTIs [81] and decreases concentrations of the NRTI zidovudine (effect not clinically significant because intracellular concentrations are not substantially changed); rifabutin decreases concentrations of NNRTIs and vice versa but has no known interaction with NRTIs; the NNRTIs efavirenz and nevirapine decrease rifabutin concentrations by inducing CYP3A [78, 79]; increases metabolism of cyclosporine, tacrolimus, sirolimus, MMF, and corticosteroids [7, 11, 82]; significant risk of graft rejection; no known interactions with azathioprine</td>
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</tr>
<tr>
<td>Pyrazinamide</td>
<td>No clinically significant interaction expected with PIs or NNRTIs; no data on NRTIs [82]</td>
<td>No known interactions with cyclosporine, tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>No known interactions with NRTIs, NNRTIs, or PIs</td>
<td>No known interactions with cyclosporine, tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>No known interactions with NRTIs, NNRTIs, or PIs</td>
<td>Nephrotoxic effects are additive with cyclosporine; close monitoring is required, and dose should be adjusted if renal function is impaired; no known interactions with tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids</td>
</tr>
<tr>
<td><strong>Second-line drugs (most commonly recommended)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones: moxifloxacin and levofloxacin</td>
<td>Moxifloxacin: no clinically significant interaction with NRTIs or NNRTIs; fluoroquinolones and the PIs atazanavir, lopinavir, and saquinavir prolong QTC interval (degree and clinical significance varies), and concomitant use may increase risk of arrhythmia [82]; levofloxacin: no known interaction with NRTIs or NNRTIs</td>
<td>Moxifloxacin: no known interaction with cyclosporine, tacrolimus, sirolimus, or azathioprine; fluoroquinolones and tacrolimus both prolong QTC interval (degree and clinical significance varies); concomitant use may increase risk of arrhythmia; fluoroquinolones may decrease serum concentration of MMF, and coadministration of fluoroquinolones and corticosteroids may increase risk of tendon damage</td>
</tr>
<tr>
<td>Ethionamide and prothionamide</td>
<td>Ethionamide is metabolized by the CYP450 system; possible interaction with antiretroviral drugs; it is unknown whether doses of ethionamide and/or certain antiretroviral drugs should be modified [78, 85]; prothionamide is structurally very similar to ethionamide, with interactions expected to be the same</td>
<td>No known interactions with cyclosporine, tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Coadministration of aminoglycosides and NRTI tenofovir is potentially nephrotoxic; avoid if possible [79, 82]; no clinically significant interaction expected with NNRTIs or PIs</td>
<td>Nephrotoxic effects are additive with cyclosporine; close monitoring is required, and dose should be adjusted if renal function is impaired [86]; no known interactions with tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids</td>
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<td>Capreomycin</td>
<td>No clinically significant interaction expected with NRTIs, NNRTIs, or PIs</td>
<td>Nephrotoxic effects are additive with cyclosporine; no known interactions with tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>No known interactions with NRTIs, NNRTIs, or PIs; CNS adverse effects of cycloserine may complicate clinical monitoring of underlying CNS disease</td>
<td>No known interactions with cyclosporine, tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids</td>
</tr>
</tbody>
</table>

Drugs for transplant recipients included: cyclosporine, tacrolimus, sirolimus, corticosteroids, mycophenolate mofetil (MMF), and azathioprine.

Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus; SOT, solid organ transplant; TB, tuberculosis. Drugs for HIV infection included nucleoside analog reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).
Table 5. Treatment of Central Nervous System Tuberculosis in Immunocompetent and Immunocompromised Hosts

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drug</th>
<th>Pediatric daily dose</th>
<th>Adult daily dose</th>
<th>CSF penetration (% CSF/Blood with inflammation)</th>
<th>Considerations for patients with HIV coinfection</th>
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<tr>
<td>First-line: 4 drugs for 2 months, then isoniazid plus rifampicin for 10 months</td>
<td><strong>Isoniazid</strong> 10–20 mg/kg (maximum, 500 mg)</td>
<td><strong>Rifampicin</strong> 10–20 mg/kg (maximum, 600 mg)</td>
<td><strong>Pyrazinamide</strong> 30–35 mg/kg (maximum, 2 g)</td>
<td>1.5 g (&lt;50 kg) or 2.0 g (≥50 kg)</td>
<td>Good (100)</td>
<td>Preferred use identical TB drug regimen in combination with ART containing efavirenz and 2 NRTIs. Some experts recommend increasing efavirenz dose to 800 mg/day in patients weighing ≥50 kg. If treatment with a PI is necessary, replace rifampin with rifabutin (less effect on levels of PIs). Reduce dose of rifabutin, usually to 150 mg 3 times a week or daily, depending on PI used. Additional combination therapy options are available. Check complete guidelines for treatment and drug-drug interactions.</td>
</tr>
<tr>
<td>MDR TB: initial therapy with 4 drugs for 6 months, followed by cultivating candidate drugs for 6-24 months total treatment duration</td>
<td>Fluoroquinolone (eg, moxifloxacin or levofloxacin)</td>
<td>Not recommended</td>
<td></td>
<td></td>
<td></td>
<td>Typically, treatment duration of ≥24 months; minimum of 18 months after sustained sputum conversion [87]</td>
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No published guidelines on management of CNS MDR TB in transplant recipients. Munoz et al suggest treating initially with 4–5 drugs (isoniazid, pyrazinamide, ethambutol, streptomycin, and/or levofloxacin) and then decreasing to 2–3 drugs (isoniazid and rifampicin) as treatment duration increases [86]. Prolonged treatment duration greater than 24 months is typically 6–24 months; minimum of 18 months after sustained sputum conversion [87]. 

No initial dose adjustment is necessary for levofloxacin, but cyclosporine or tacrolimus concentrations should be monitored [84]. Amikacin or streptomycin should be included in the regimen for at least the first 2 months [13]. 

CID IMMUNOCOMPROMISED HOSTS

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</table>
Adjunctive corticosteroids: recommended for all patients with TB meningitis, regardless of severity; also recommended for tuberculoma and TB radiculomyelitis, but based on limited evidence.

<table>
<thead>
<tr>
<th>Drug</th>
<th>14 years:</th>
<th>&gt;14 years:</th>
<th>Generally recommended for patients with HIV coinfection, but evidence is inconclusive. When IRIS is present or suspected, dexamethasone should be initiated at 4 mg 4 times daily and continued until clinical and radiographic improvement (typically decreased contrast enhancement) is seen; steroids should then be tapered gradually over 3–4 months. If symptoms or enhancement worsen, restart therapy or increase dosage and continue for another 3–4 months before reinitiating taper.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>0.6 mg/kg (intravenous or PO) for 4 weeks, then reduce course over next 4 weeks</td>
<td>stage I TB meningitis: 0.3 mg/kg in week 1, 0.2 mg/kg in week 2, and then 4 weeks of oral therapy; stage II/III: 0.4 mg/kg initially, then reduce course over 6–8 weeks</td>
<td>[89]</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4 mg/kg (PO or intravenous) for 4 weeks, then reduce course over next 4 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This table, adapted from British Infection Society guidelines [90] and from Rock et al [2], is for summary and review purposes only. For detailed information and guidelines, refer to the guidelines from the Centers for Disease Control and Prevention (CDC) [91], the American Thoracic Society [81], the British Infection Society [90], the World Health Organization (WHO) [92, 93], and other resources.

Abbreviations: ART, antiretroviral therapy; CNS, central nervous system; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome; MDR, multidrug resistant; NRTI, nucleoside analog reverse-transcriptase inhibitor; PI, protease inhibitor TB, tuberculosis.

* These recommendations are from the British Infection Society guidelines for the diagnosis and treatment of CNS TB in adults and children [90]. In 2003 the CDC recommended an identical regimen, except that the continuation phase of isoniazid and rifampicin may last for 7–10 months [91]. Some experts recommend continuing pyrazinamide for the full duration of therapy owing to concerns about poor penetration of rifabutin once inflammation subsides [94].

* Plasma therapeutic drug concentrations may be monitored to determine whether further dose adjustment is necessary.

* For more information on drug interactions and dosing, see www.hiv-druginteractions.org and the CDC guidelines for managing drug interactions in the treatment of HIV-related TB [78].

* In 2010 the WHO recommended replacing ethambutol with streptomycin in patients with TB meningitis [92].

* Cycloserine has good CNS penetration and may also be considered for MDR TB treatment. Intrathecal amikacin and levofloxacin have been successfully used in combination for MDR TB meningitis [73].

* Grading system based on modified British Medical Research Council criteria: grade I, Glasgow Coma Scale score of 15 with no focal neurologic signs; grade II, score of 11–14, or 15 with focal neurologic signs; grade III, score of ≤10 [95].
with tuberculous meningitis to reduce death and disabling residual neurologic deficit among survivors” [74]. Potential harms of corticosteroids include decreased penetration of antituberculous medications due to reduced meningeal inflammation, immunosuppression, and gastrointestinal bleeding. Although no randomized controlled trial of steroids has been performed for patients with tuberculoma, most experts recommend co-administration of steroids with antituberculous therapy [75–77].

The most significant drug-drug interactions in HIV-infected patients with TB are due to the rifamycins, which decrease serum concentrations of protease inhibitors and some non-nucleoside reverse-transcriptase inhibitors through induction of the liver enzyme cytochrome P450 and its isoform CYP3A4 [78, 79]. Drug-drug interactions between medications for TB, HIV infection, and SOT are listed in Table 4. Table 5 provides a summary of treatment guidelines for CNS TB in both immunocompetent and immunosuppressed patients.

### HIV-Infected Patients

For patients with pulmonary TB and HIV infection who have not recently initiated antiretroviral therapy (ART), emerging evidence supports early initiation of ART to reduce mortality—especially in patients with CD4 cell counts <50 cells/mm³—despite the increased incidence of IRIS (see section below) [96]. The WHO recommends initiation of ART after starting TB treatment irrespective of CD4 cell count (Table 6); however, timing of ART initiation in patients with TB meningitis was not addressed and may differ, as discussed below [90, 98].

A study of TB meningitis in HIV-infected people in Vietnam compared immediate vs. delayed (2 months) initiation of ART for patients with TB meningitis and found no significant difference in mortality; however, patients who initiated ART immediately had higher rates of serious (grade 3 or 4) adverse events. Due to rapidity of death, the authors were unable to determine if these severe reactions were due to IRIS [99].

Two large clinical trials of pulmonary TB in HIV-infected people (SAPIT and the ACTG 5221 STRIDE study) reported ART initiated within 4 weeks of starting TB treatment, in patients with CD4 count <50 cells/mm³, reduced mortality by 68% and 58%, respectively. In both studies, early initiation of ART in people with CD4 cell counts <50 cells/mm³, was associated with higher rates of IRIS (2.2 times and 2.5 times, respectively) and of switching ≥1 antiretroviral medication due to medication toxicity [100, 101]. The Cambodian Early versus Late Introduction of Antiretroviral Drugs (CAMELIA) study enrolled 661 patients with <200 CD4 cells/µL receiving treatment for TB and randomly assigned them to initiate ART either 2 or 8 weeks later. After 50 weeks of follow-up, 59 (17.8%) of 332 participants who started ART 2 weeks after beginning TB treatment had died, while 90 (27.4%) of 329 participants who started ART 8 weeks after beginning TB treatment had died. Of note, none of these studies included people with CNS TB [102].

In some regions of the world, HIV-infected individuals have higher rates of CNS MDR TB, compared with HIV-negative patients, with rates up to 7–12.5% [23, 26, 103] CNS MDR TB in HIV-infected individuals has higher mortality rates and is particularly challenging to treat due to poor CNS penetration of many second-line TB medications [14]. For patients with MDR TB, earlier initiation of ART and prolonged treatment improves survival—see guidelines published elsewhere [78, 87].

### HIV Infection and Immune Reconstitution Inflammatory Syndrome

With the widespread availability of ART, IRIS complicates the diagnosis and treatment of CNS TB [104]. Mycobacterial infections comprise ~40% of IRIS cases and cause either unmasking of a subclinical infection or paradoxical recurrence of a previously treated infection. Paradoxical recurrence is driven by antigen-specific immune response to viable bacilli, dead organisms, or remaining antigen; cultures may be negative owing to previous treatment. In a study of 258 patients with pulmonary TB, paradoxical IRIS occurred in 53 (20.5%) and in an additional 8 (3.1%) later during treatment; 6 (10%) of patients with IRIS died [105]. A review of 166 published cases of IRIS associated with mycobacterial infections found that CD4 counts <50 cells/µL, initiation of ART within 2 months of TB treatment, and rapid fall in viral load were risk factors [9]. In the largest series of IRIS affecting the CNS, the median onset of symptoms was 14 days after the beginning of ART [57].

IRIS is particularly worrisome in patients with tuberculoma, in whom new or expanding lesions may cause mass effect, seizures, and clinical deterioration [106, 107]. Compared with tuberculomas in HIV-infected patients not receiving ART, tuberculomas in patients with IRIS have increased perilesional inflammation [107].

Findings in patients with paradoxical TB-associated IRIS (but not CNS TB) and in a series of patients with paradoxical neurologic TB-associated IRIS suggested that steroids improve

### Table 6. Initiation of Antiretroviral Therapy in Patients With HIV and Central Nervous System Tuberculosis, According to CD4 Count

<table>
<thead>
<tr>
<th>CD4 count, cells/µL</th>
<th>Recommended begin ART (per CDC and WHO guidelines)</th>
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<tbody>
<tr>
<td>&gt;500</td>
<td>Within 8 weeks of starting TB treatment</td>
</tr>
<tr>
<td>200–500</td>
<td>Within 2–4 weeks of starting TB treatment or by 8 weeks at latest</td>
</tr>
<tr>
<td>&lt;200</td>
<td>Within 2–4 weeks of starting TB treatment</td>
</tr>
</tbody>
</table>

* Table adapted from World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) guidelines [92, 97]. See article by Wells [87] for information on when to initiate ART in patients with multidrug-resistant TB.

Abbreviations: ART, antiretroviral therapy; CNS, central nervous system; HIV, human immunodeficiency virus; TB, tuberculosis.
morbidity and mortality [57, 107]. In a study of 23 patients with CNS TB-associated IRIS, 21 (91%) received corticosteroids for a median of 58 days (range, 1–49 weeks), and 16 (70%) were still alive at 6 months [57]. Because corticosteroids are recommended for treatment of CNS TB, the same dosing should be useful for preventing IRIS, but prolonged duration and slower incremental tapering is recommended to avoid clinical deterioration.

Transplant Recipients
Treatment of CNS TB in transplant recipients is especially challenging because many TB medications interact with immunosuppressive agents. Rifampicin, in particular, may accelerate the metabolism of cyclosporine, tacrolimus, and corticosteroids and can lead to allograft rejection and higher mortality [7, 11]. Coadministration of rifampicin and cyclosporine is typically avoided, although they may be used together if dosages of both medications are increased [11]. Rifabutin may be used as an alternative to rifampicin because it has less cytochrome p450 induction and theoretically less effect on levels of certain immunosuppressants [7]. Rifampicin, and possibly isoniazid, can increase corticosteroid catabolism and thus affect the level of immunosuppression [109].

Hepatotoxicity is a significant concern in transplant recipients receiving antituberculous therapy, especially after liver transplantation. In one series, hepatotoxicity occurred in 83% of liver transplant recipients after standard TB induction therapy [109]. SOT recipients are at high risk of INH and rifampicin hepatotoxicity, particularly when INH is given as part of a multidrug regimen rather than as a single drug for prophylaxis [11, 13]. MDR TB is rare in transplant recipients (reported incidence, <2%) but will probably increase as transplant programs expand in developing countries [13].

IRIS or paradoxical worsening of pulmonary TB (but not CNS TB) has been described in transplant recipients receiving anti-TB therapy. The time course—within 1–2 months after initiation of anti-TB treatment—and mechanism seem to be similar to HIV-related IRIS. If IRIS is severe, the dose of steroids may be temporarily increased to counteract the exaggerated immune response [110].

OUTCOME
In immunocompetent patients, worse outcome of TB meningitis is correlated with greater neurologic impairment at presentation [2, 41, 48] as well as with the presence of hydrocephalus [30, 111]. Most studies have reported higher mortality rates in HIV-infected patients, with some reporting up to 65% [26, 27, 30, 71]. Factors associated with poor prognosis of TB meningitis in HIV-infected patients include more severe illness at presentation, CD4 cell count <50 cells/μL, and presence of MDR strains [26, 112]. Mortality from tuberculoma is <10% with appropriate antituberculous therapy [31]. Clinical improvement is often delayed and may occur after ≥3 months of treatment [113]. In a small case series of tuberculoma in HIV-infected and HIV-uninfected patients mortality rates were similar in both groups [35]. Because published reports on TB abscess consist mainly of case reports and series, overall mortality rates are not well defined. One review of HIV-infected patients with TB abscess reported that 3 (25%) of 12 HIV patients died within 6 months of follow-up [40].

TB mortality in transplant recipients is high, ranging from 13% to 40% [12]. Disseminated infection, lung transplantation, and receipt of muromonab-CD3 are significantly correlated with higher mortality [7, 11]. Patients who develop TB within the first year after transplantation are more likely to have extrapulmonary manifestations and are at greater risk of death [114].

CONCLUSIONS
CNS TB causes significant morbidity and mortality and is difficult to diagnose and treat. Immunosuppression due to HIV infection or immunosuppressive therapy after transplantation significantly increases the risk of acquiring CNS TB, complicates the clinical presentation, diagnosis, and treatment, and poses a challenge to the clinician attempting to differentiate CNS TB from other potential opportunistic infections.

With some exceptions noted above, HIV infection does not typically alter the radiographic or neurologic presentation of CNS TB; however, CSF pleocytosis is often absent, and patients with CD4 counts <50 cells/μL tend to have abnormal CSF findings less frequently. When a high suspicion for CNS TB is present, further CSF and ancillary testing should be performed and empiric treatment considered, especially if the patient is from an area with endemic TB or has evidence of TB outside of the CNS. ART and IRIS can affect the manifestations and outcome of CNS TB infection.

Physicians treating HIV-infected patients and SOT recipients with CNS TB should be aware of common drug interactions, benefits of adjunctive use of steroids for TB meningitis and IRIS, and lack of consensus regarding timing for initiation of ART. With increased attention to TB diagnosis and treatment from international funding agencies, there is hope that the diagnosis and treatment of CNS TB will become easier and more effective in the near future.

Notes

Acknowledgments. The authors thank Christopher Spitters, MD, MPH, MA, Tuberculosis Clinic, Seattle King County Department of Public Health; Douglas Black, PharmD, University of Washington School of Pharmacy; Thomas O. McPharlin, RPh, University of Washington School of Pharmacy; and Charles A. Peloquin, PharmD, FCCP, Infectious Disease Pharmacokinetics Laboratory, University of Florida College of Pharmacy,
and Emerging Pathogens Institute, Gainesville, for their expert opinions and valuable input.

Financial support. This work was supported by the Office of the Director, National Institutes of Health (NIH), Fogarty International Center, Office of AIDS Research, National Cancer Center, National Eye Institute, National Heart, Blood, and Lung Institute, National Institute of Dental and Craniofacial Research, National Institute on Drug Abuse, National Institute of Mental Health, National Institute of Allergy and Infectious Diseases, and NIH Office of Women’s Health and Research through the International Clinical Research Fellows Program at Vanderbilt University (grants R24 TW007988 [subcontract] and RO1NS55627 to J. R. Z.).

Potential conflicts of interest. All authors: No reported conflicts.
All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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