Objectives

1. Present an overview of normal neurodevelopment in children.
2. Describe how human immunodeficiency virus (HIV) affects the nervous system.
3. Discuss how to monitor neurodevelopment in HIV-infected children.
4. Review common nervous system abnormalities in children with HIV infection.
5. Review guidelines for the diagnosis and management of children with neurologic and psychiatric manifestations of HIV.

Key Points

1. HIV can profoundly affect the developing nervous system.
2. Monitoring the development of HIV-infected children is essential.
3. Children with HIV are at increased risk of developing a variety of infectious and noninfectious abnormalities of the nervous system.
4. Prompt diagnosis and treatment of many nervous system abnormalities can significantly affect long-term outcomes.

The nervous system is a major target of human immunodeficiency virus (HIV) infection, and the consequences of nervous system involvement are often serious. Clinically significant nervous system involvement most often occurs in conjunction with profound immunosuppression and in the presence of other AIDS-defining illnesses. HIV-associated neurologic disorders can, however, be the first problems with which children and adults with AIDS appear for treatment. A variety of abnormalities of the central nervous system (CNS) and peripheral nervous system (PNS) are associated with HIV and AIDS. These abnormalities may be attributable to the following causes:

- HIV’s direct effects on the nervous system
- Opportunistic infections and malignancies occurring because of immunosuppression
- Neurotoxic effects of antiretroviral treatments
- Other systemic complications of HIV that affect brain function.

Neurologic disorders in people with HIV infection include peripheral neuropathies (nerve disorders that affect the feet, hands, and limbs), myelopathy (disorders of the spinal cord), focal cerebral mass lesions (brain tumors such as CNS lymphoma), CNS complications of opportunistic infections, vascular (blood vessel) abnormalities, seizures, and encephalopathy. Children and adults with HIV often suffer similar neurologic and psychiatric manifestations. However, because children’s nervous systems are still growing and developing, special attention must be paid to the early detection of neurologic problems in pediatric patients. Early detection and appropriate treatment of HIV-associated neurologic problems in children often leads to favorable outcomes.

HIV has been found in the brain and spinal fluid of children infected by HIV. The neurons themselves are not infected by HIV, but neuronal function is impaired via complex mechanisms. Other cells in and around the brain such as microglia, astrocytes, oligodendroglia, and cells of the monocyte-macrophage lineage have CD4 receptors, allowing for direct infection by the virus. Monocytes and microglial cells serve as the main CNS reservoirs for HIV. Once infected, these cells secrete several substances (e.g., tumor necrosis factor α and nitric oxide) that are toxic to the brain. HIV-infected microglial cells secrete chemokines that amplify recruitment of HIV-infected monocytes, leading to a self-perpetuating feedback loop. The viral coat protein, gp120, can enter the CNS independent of the rest of the virus and is directly neurotoxic. Brain endothelial cells react to substances associated with HIV infection, such as Tat and cytokines, by releasing neurotoxic substances at the surface abutting the brain. A selective barrier (the blood-brain barrier [BBB]) between circulating blood and brain tissues prevents many damaging substances from reaching the brain. Certain compounds readily cross the
Neurologic and psychiatric manifestations of pediatric HIV infection can be either sudden or gradual in onset. In children, the effects of HIV infection on the brain often manifest as a failure to reach age-appropriate developmental milestones. Brain growth and head size may also be affected in young children. Careful clinical evaluations are necessary to ensure that these manifestations do not go unnoticed. Clinicians must maintain a high index of suspicion for neurologic abnormalities in children with HIV and must ask appropriate questions to ensure that neurologic, psychiatric, and developmental problems in children are promptly recognized.

Neurodevelopmental Assessment

People who provide health care to children must understand basic principles of neurodevelopmental assessment. This understanding is especially important for those providing care to HIV-infected children because neurodevelopmental delays are often early signs of disease progression. Neurodevelopmental difficulties can be the first indicator of a CNS abnormality.

Many standardized tools have been developed for screening neurodevelopment. Because some children may not have regular exposure to elements of standardized screening tools, these tools may underestimate the knowledge and abilities of children in certain cultures. Cultural practices may influence the “normal” age of development for even basic motor tasks such as crawling and walking. Therefore, whenever possible, one should use a tool that has been researched and validated for use among children of similar backgrounds.

When standardized tools are unavailable or time does not permit their widespread use, medical providers should keep a simple record of the developmental milestones achieved by their pediatric patients. Failure to achieve key milestones by certain ages can be considered “red flags” that should alert medical practitioners to the need for further evaluation and the consideration of interventions such as highly active antiretroviral therapy. Tables 1 and 2 provide basic guidelines for normal milestone progression in young children. Older children can be compared with their same-age peers to give an indication of whether they are functioning appropriately. Asking simple questions regarding children’s learning in the classroom, whether they can perform necessary activities of daily living and whether they interact appropriately with others can give valuable insight into a child’s development. Sustained developmental regressions (loss of the ability to perform previously acquired skills) are never normal and should prompt appropriate additional evaluations and interventions.

Children who fail to reach age-appropriate milestones as expected should be evaluated for conditions that lead to developmental and neurological deficits. Neurodevelopmental delays may also be related to factors other than HIV such as environmental, psychosocial, and nutritional factors. Whenever possible, neurodevelopmental testing should be coordinated with a comprehensive history, clinical examination, and laboratory data to confirm the appropriate diagnosis.

Neurodevelopmental Delays in HIV-Infected Children

Cognitive delays are common among HIV-infected infants and young children. Sometimes the problems are subtle. They may manifest as deficits in attentional focus and executive functioning, which refers to the ability to direct one’s actions to actively solve a problem. Children with these problems may be more distractible and impulsive, have difficulties planning and organizing, and be inefficient problem solvers. Deficits in visual–spatial processing, visual–motor integration, and fine-motor skills have also been demonstrated among HIV-infected children and can manifest as difficulties with mathematics, poor handwriting, and problems completing certain activities of daily living (e.g., dressing). The domain-specific deficits mentioned here are thought to relate to abnormalities in the brain’s white matter, frontal system, and basal ganglia. Medical providers must consider domain-specific functioning among HIV-infected patients because deficits in these areas can have pervasive effects on daily functioning in home, school, and social settings.

If neurodevelopmental weaknesses occur, several options exist for intervention, ranging from therapeutic services to environmental support. Even in low-resource settings,
<table>
<thead>
<tr>
<th>Age</th>
<th>Psychosocial</th>
<th>Gross Motor</th>
<th>Fine-Motor</th>
<th>Communication/Cognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>• Follows faces to the midline</td>
<td>• Moves all extremities</td>
<td>• Opens hands spontaneously</td>
<td>• Started by loud sounds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lifts head when lying on stomach</td>
<td></td>
<td>• Cries</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Quiets when fed and comforted</td>
</tr>
<tr>
<td>2 mo</td>
<td>• Follows faces past midline or touch</td>
<td>• Lifts head up 45° when on stomach</td>
<td>• Looks at own hand</td>
<td>• Coos, squeals, gurgles</td>
</tr>
<tr>
<td></td>
<td>• Smiles responsively</td>
<td></td>
<td>• Looks at close objects</td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>• Recognizes mother</td>
<td>• Supports head for a few seconds when upright</td>
<td>• Opens hands frequently</td>
<td>• Responds to voices</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Laughs</td>
</tr>
<tr>
<td>4 mo</td>
<td>• Recognizes parent’s voice or touch</td>
<td>• Bears weight on legs</td>
<td>• Clasps hands</td>
<td>• Turns head to sound</td>
</tr>
<tr>
<td></td>
<td>• Follows an object with eyes for 180°</td>
<td>• Good neck control when pulled to sitting position</td>
<td>• Grabs a small object</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Anticipates food on sight</td>
<td>• Can lift chest and support self on elbows when lying on stomach</td>
<td>• Reaches for object</td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>• Reaches for familiar people</td>
<td>• Rolls from stomach to back or vice versa</td>
<td>• Plays with hands by touching them together</td>
<td>• Responds to name</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sits with support</td>
<td></td>
<td>• Babbles</td>
</tr>
<tr>
<td>9 mo</td>
<td>• Indicates wants</td>
<td>• Sits without support</td>
<td>• Takes toy in each hand</td>
<td>• Imitates speech sounds</td>
</tr>
<tr>
<td></td>
<td>• Waves &quot;bye-bye&quot;</td>
<td>• Creeps or crawls</td>
<td>• Transfers toy from one hand to the other</td>
<td>• Understands &quot;no&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Has stranger anxiety</td>
<td></td>
<td>• Looks for a toy when it has fallen or is hidden</td>
</tr>
<tr>
<td>12 mo</td>
<td>• Has separation anxiety</td>
<td>• Pulls self up to standing position</td>
<td>• Precise pincher grasp</td>
<td>• Says “mama” or “dada” and one other word</td>
</tr>
<tr>
<td></td>
<td>• Imitates gestures</td>
<td>• Walks with support</td>
<td>• Bangs blocks together</td>
<td>• Finds hidden objects easily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Explores objects in different ways (shakes, bangs, drops)</td>
</tr>
<tr>
<td>15 mo</td>
<td>• Explores people and surroundings</td>
<td>• Takes steps on own</td>
<td>• Can stack one cube on another</td>
<td>• Says “mama” and “dada” to respective parents</td>
</tr>
<tr>
<td></td>
<td>• Imitates activities/speech</td>
<td>• Gets to a sitting position from a lying position</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 mo</td>
<td>• Calls adult to initiate interactions</td>
<td>• Walks without help</td>
<td>• Takes off own shoes</td>
<td>• Says several single words</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Feeds self</td>
<td>• Attends to pictures in a book</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Identifies body parts</td>
</tr>
<tr>
<td>2 yrs</td>
<td>• Tries to please others</td>
<td>• Runs without falling</td>
<td>• Imitates drawing a vertical line</td>
<td>• Combines two words</td>
</tr>
<tr>
<td></td>
<td>• Engages in parallel (imitative) play</td>
<td></td>
<td></td>
<td>• Attends to simple story</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Recognizes several common objects</td>
</tr>
<tr>
<td>3 yrs</td>
<td>• Takes turn in games</td>
<td>• Runs easily</td>
<td>• Can build a tower of more than six blocks</td>
<td>• Vocabulary of hundreds of words</td>
</tr>
<tr>
<td></td>
<td>• Plays make-believe with toys and people</td>
<td>• Kicks ball</td>
<td>• Can draw a vertical line, horizontal line and circular strokes</td>
<td>• Uses four- to five-word sentences</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Nearly all speech is intelligible to others</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Can sort objects by shapes and colors</td>
</tr>
<tr>
<td>4 yrs</td>
<td>• Engages in fantasy play; may have imaginary friends</td>
<td>• Can hop on 1 foot</td>
<td>• Can draw circles and squares</td>
<td>• Tells stories</td>
</tr>
<tr>
<td></td>
<td>• More independent</td>
<td>• Can go upstairs/downstairs without help</td>
<td></td>
<td>• Names some colors</td>
</tr>
<tr>
<td>5 yrs</td>
<td>• Wants to be like friends</td>
<td>• Jumps, climbs</td>
<td>• Can learn to tie shoelaces</td>
<td>• Composes six- to eight-word sentences with all parts</td>
</tr>
<tr>
<td></td>
<td>• Questions others</td>
<td>• Can stand on one foot for 10 s or longer</td>
<td>• Can use fork and spoon</td>
<td>• Recalls part of a story</td>
</tr>
<tr>
<td>6-12 yrs</td>
<td>• Peer groups become important</td>
<td>• Can participate in team sports</td>
<td>• Uses hands like adults, quickly and easily</td>
<td>• Learns to read</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Executive functioning skills improve (e.g., planning, problem-solving)</td>
</tr>
</tbody>
</table>
one can take many measures to support children with neurodevelopmental problems. Behavioral strategies such as using firm limits to deter impulsive behaviors and providing tangible rewards to reinforce positive behaviors should be suggested by practitioners who recognize children with impulse-control and attention problems. Health care practitioners and families can also suggest environmental modifications such as sitting near the teacher or giving more time to complete school exams. Families and community members can also give children extra help with study skills and organizing their activities of daily living when needed. By recognizing deficits and educating families regarding simple interventions that can be undertaken at home and school, health practitioners can help children to maximize their potential. When developmental problems are identified and services are available, referrals for physical therapy, occupational therapy, speech therapy, and/or neuropsychologic evaluations can be helpful.

CNS and PNS Abnormalities

HIV Encephalopathy
HIV encephalopathy is defined by one or more of the following, progressing over at least 2 months in the absence of another causative illness:
- Failure to attain, or loss of, developmental milestones or intellectual ability
- Progressive impaired brain growth
- Acquired symmetric motor deficit accompanied by paresis, pathological reflexes, ataxia, and/or gait disturbances

HIV-related encephalopathy can occur without other signs and symptoms. Periodic neurologic and cognitive assessment can help with the recognition and monitoring of HIV encephalopathy. HIV-infected children with HIV encephalopathy can proceed along a variable neurodevelopmental course, with periods of spontaneous improvement and stabilization. Treatment with antiretroviral medications and early intervention programs for children with neurologic impairments and developmental delays can help mitigate the symptoms and improve the course of HIV encephalopathy.

Impaired brain growth in children with HIV encephalopathy can be observed both clinically and radiographically. In children younger than 2 years, a plateau in serial measurements of head circumference is an indicator of impaired brain growth. In older children whose cranial sutures are closed, measurements of head circumference are not as useful. If available, computed tomography imaging may be used to detect loss of brain tissue. Radiological findings may demonstrate signs of cerebral atrophy: enlargement of the sulci, the subarachnoid space, and the ventricles. Brain atrophy is a significant predictor of HIV-related disease progression. Calcification

Table 2. Developmental red flags

<table>
<thead>
<tr>
<th>Age</th>
<th>Developmental Problem</th>
</tr>
</thead>
</table>
| Birth-3 mo   | • Failure to alert to environmental stimuli  
• Rolling over before 2 mo (indicates hypertonia)  
• Persistent fisting at 3 mo                                                                 |
| 4-6 mo       | • Poor head control  
• Failure to smile  
• Failure to reach for objects by 6 mo                                                                 |
| 6-12 mo      | • No baby sounds or babbling by 8 mo; no single words by 12 mo  
• Does not bear some weight on legs by 7 mo; cannot stand with support by 12 mo  
• Does not follow objects with both eyes at near and far (6 ft) ranges  
• Does not gesture or point by 12 mo                                                                 |
| 12-24 mo     | • Cannot walk by 18 mo  
• Hand dominance prior to 18 mo (may indicate weakness on the non-dominant side)                                                                 |
| 2-3 yrs      | • Unable to communicate in short phrases  
• Little interest in other children  
• Frequent falling by end of 3 yrs                                                                 |
| 3-4 yrs      | • Cannot grasp a crayon between thumb and fingers by end of 4 yrs  
• No interest in interactive games                                                                 |
| 4-5 yrs      | • Unable to concentrate on single activity for more than 5 min  
• Cannot understand two-part commands (e.g., “pick up the cup and put it on the table”)                                                                 |
| Any age      | • Loss of previously attained milestones                                                                 |
of the basal ganglia can be seen with HIV encephalopathy. Neuroimaging can also help exclude other disease processes.

**Seizures**
Seizures in children with HIV infection can have a variety of causes. Seizures in the context of HIV should raise suspicion of intracranial opportunistic infections, mass lesions, and vasculopathies. Metabolic imbalances, drug side effects or interactions, and cortical structural changes can also trigger seizures. Suspicion of a focal CNS lesion should be heightened whenever a focal neurologic deficit is discovered on history, physical exam, or electroencephalogram.

Unless neuroimaging (computed tomography or magnetic resonance imaging) is available, determining the etiology of seizures may be difficult. Laboratory studies may detect electrolyte or metabolic imbalances, and lumbar puncture may help to confirm suspected infection.

Anticonvulsant medications can help to control seizures. Their use in HIV-positive patients should be coordinated by providers knowledgeable about possible interactions between anticonvulsants and antiretroviral medicines.

**Strokes**
Strokes are more commonly seen in children with advanced HIV disease. HIV produces inflammation of blood vessels, including those in the brain. Children with HIV are at an increased risk of suffering strokes caused by the effects of HIV on the vessels of the brain. Many cases of stroke are hemorrhagic, which is sometimes related to HIV-associated thrombocytopenia, idiopathic thrombocytopenic purpura, or CNS neoplasia. Whenever possible, investigations should be carried out.

**Figure 1. Progressive HIV Encephalopathy.** This is a 5-year-old girl with HIV infection and severe, progressive HIV encephalopathy. The girl is non-communicative and spastic. This condition may progress rapidly for a period of time and then stabilize or improve spontaneously.

**Figure 2. Generalize Brain Atrophy.** This is a computerized tomographic (CT) scan of the brain of an 8-year-old boy with HIV infection and generalized brain atrophy. Cerebral atrophy is observed commonly among children with HIV-associated encephalopathy, but it also may be observed among children who are normal neurologically and developmentally.
to determine the underlying cause of a stroke. Correction of the underlying cause may help to prevent subsequent episodes.

When thrombotic strokes occur, low-dose aspirin given for at least 6 months can help prevent subsequent strokes. In settings where anticardiolipin antibodies and antiphospholipid antibodies can be measured, these approaches can be helpful for deciding when to discontinue aspirin therapy after a thrombotic event. If these antibody levels are abnormal after the event, some experts would recommend discontinuation of prophylactic aspirin after the levels normalize, provided that the patient has been on aspirin for at least 6 months.

Opportunistic Infections
Opportunistic infections (OIs) that involve the CNS are often not readily apparent and should be considered in cases of acute or chronic behavioral or mental status changes, as well as in children with persistent headaches, malaise, or fever. The most common pathogens that cause CNS infections in immunocompromised patients include Cryptococcus neoformans, herpes simplex virus, Toxoplasma gondii, and cytomegalovirus (CMV). JC virus, which leads to progressive multifocal demyelinating leukoencephalopathy in about 5% of adults with AIDS, is rarely found in children.

HIV-infected children who develop OIs in the CNS may develop signs of increased intracranial pressure (severe headache, nausea, vomiting, confusion, coma), focal neurologic signs (hemiparesis, visual changes, gait instability, fine or gross motor abnormalities), malaise, fever, behavioral or personality changes, seizures, and meningeal signs (headache, neck pain, and nuchal rigidity). Table 3 provides guidance regarding the diagnosis of CNS infections in patients with HIV.

Table 4 provides treatment options for the empiric management of CNS infections. When possible, cultures of the CNS should be obtained before initiating antibiotics for suspected bacterial meningitis. The recommended duration of treatment varies depending on the organism identified. When bacterial meningitis is suspected and cultures are not available, treatment should be continued for 3 weeks in neonates and 10 days in older children. In countries where Haemophilus influenzae type B (Hib) vaccine is not given, steroids are more likely to be of benefit when given at the beginning of meningitis treatment, particularly in children younger than 2 years.

The neurologic impairment most frequently observed in children with HIV is caused by HIV infection itself rather than by OIs or CNS tumors. CNS OIs must always be considered in HIV-infected children with CNS manifestations; if these infections go untreated, death may occur.

CNS Neoplasms
Non-Hodgkin’s lymphoma is the most common CNS neoplasm in children with AIDS. CNS lymphomas may be confused with other CNS conditions, such as toxoplasmosis or cryptococcosis. They tend to grow rapidly and to lead to headaches, nausea/vomiting (primarily upon arising in the morning), altered mental status, focal neurologic signs, and increased intracranial pressure. Epstein-Barr virus infection is involved with the pathogenesis of non-Hodgkin’s lymphoma in HIV-infected children. Highly active antiretroviral therapy and anticancer chemotherapies, including corticosteroids, can improve prognosis.

Leiomyosarcomas have been reported with increased frequency in children with HIV infection. The most common sites of the lesion are the lungs, spleen, and gastrointestinal tract. Leiomyosarcomas can be found in the brain as well. Symptoms of intracranial leiomyosarcoma are the same as those seen with other CNS mass lesions.

Table 5 compares common features of HIV-associated CNS mass lesions to assist with the differential diagnosis of affected patients.

HIV Myopathy
This module includes myopathy because it is often part of the differential diagnosis when neurologic problems are being considered. Myopathy is characterized by muscular pain and proximal muscle weakness. HIV-associated myopathy is more common in adults than in children. With the increased use of antiretroviral nucleoside analogues (e.g., zidovudine) in children, however, myopathies are occurring more frequently as a side effect of these medications. Myopathy can also be caused by direct effects of the virus or by secondary infections (e.g., CMV). Diagnosis of myopathy may be made based on clinical observations and elevated creatine kinase
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Common Clinical Features</th>
<th>Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial meningitis</strong></td>
<td>Fever&lt;br&gt;Nuchal rigidity&lt;br&gt;Nausea/vomiting&lt;br&gt;Irritability or restlessness&lt;br&gt;Anorexia or poor feeding&lt;br&gt;Headache or bulging fontanelle&lt;br&gt;Confusion or change of behavior&lt;br&gt;Photophobia</td>
<td>CSF: usually elevated opening pressure, elevated WBCs, neutrophil predominance, elevated protein, low glucose, organisms on Gram stain and/or culture. If LP cannot be obtained immediately: obtain a blood culture, then begin antibiotics immediately</td>
</tr>
<tr>
<td><strong>Mycobacterium tuberculosis</strong></td>
<td>Meningitis with subacute onset, not responding to standard antibiotics; sometimes with focal findings due to CNS tuberculoma&lt;br&gt;Other signs suggestive of TB:&lt;br&gt;  • Persistent and unremitting cough&lt;br&gt;  • Failure to gain weight or weight loss&lt;br&gt;  • Fever</td>
<td>CSF usually elevated opening pressure with lymphocytosis, elevated protein, low glucose. AFB/TB culture insensitive. Evidence of TB elsewhere (by CXR, sputum/gastric aspirate, etc.). CT where available: obstructive hydrocephalus, basilar meningeal enhancement. TB skin test and history of TB contact can be helpful.</td>
</tr>
<tr>
<td><strong>Cryptococcal meningitis</strong></td>
<td>Common features:&lt;br&gt;Subacute onset&lt;br&gt;Fever&lt;br&gt;Headache&lt;br&gt;May also have:&lt;br&gt;  • Nuchal rigidity&lt;br&gt;  • Nausea and vomiting&lt;br&gt;  • Altered level of consciousness&lt;br&gt;  • Impaired mental function&lt;br&gt;  • Cranial nerve lesions&lt;br&gt;  • Visual deficits&lt;br&gt;CD4 &lt;100 cells/mL or equivalent percentage for age</td>
<td>CSF: elevated opening pressure, mononuclear cell predominant, elevated protein, low glucose, India ink +, cryptococcal antigen from CSF/serum +. CSF may appear normal in &gt;50% of cases. CT: communicating hydrocephalus, pseudocysts, mass lesions.</td>
</tr>
<tr>
<td><strong>Toxoplasma encephalitis</strong></td>
<td>Headache&lt;br&gt;Confusion&lt;br&gt;Fever&lt;br&gt;Lethargy&lt;br&gt;Focal neurologic signs (hemiparesis, cranial nerve palsies, ataxia, sensory deficits)&lt;br&gt;May have seizures, associated hepatic involvement, pneumonitis, myocarditis&lt;br&gt;Intracranial mass lesions&lt;br&gt;Ocular:&lt;br&gt;  • Marked loss of central vision&lt;br&gt;  • Hazy vision&lt;br&gt;  • “Floaters”&lt;br&gt;CD4 &lt;100 cells/mL or equivalent percentage for age</td>
<td>Presumptive on clinical and radiographic findings in context of T. gondii IgG seropositivity. CT with consistent lesions. Organisms in tissue or body fluids (e.g., CSF). Ophthalmologic exam: white or yellowish foci with elevated, edematous margins, surrounded by a zone of hyperemia (active lesion).</td>
</tr>
<tr>
<td><strong>CMV</strong></td>
<td>Retinitis:&lt;br&gt;  • Changes in visual acuity&lt;br&gt;  • Sees “floaters”&lt;br&gt;  • Acquired inability to fix and follow (small infants)&lt;br&gt;  • Abnormal light reflexes (small infants)</td>
<td>Ophthalmologic exam: yellowish-white granular areas with perivascular exudates and hemorrhage. Histology: coagulation necrosis, microvascular abnormalities.</td>
</tr>
</tbody>
</table>

*Continued on next page*
### Table 3. Diagnosis of CNS infections in children with HIV (continued)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Common Clinical Features</th>
<th>Diagnostics</th>
</tr>
</thead>
</table>
| CMV (continued) | Subacute or chronic encephalitis/ventriculitis:  
- Weakness  
- Confusion  
- Loss of developmental milestones  
Axonal polyradiculopathy:  
- Painful, ascending muscle weakness  
- Loss of deep tendon reflexes  
- Loss of bladder/bowel control  
CD4 <50 cells/mL or equivalent percentage for age | Confirms infection but not disease:  
anti-CMV antibodies if >12 mo  
CSF pleocytosis in 50%, frequently PMN predominance, elevated protein, occasionally with low glucose, CMV DNA by PCR |
| HSV encephalitis | Acute or subacute encephalitis  
- Fever  
- Altered level of consciousness  
- Headache  
- Behavior changes  
- Seizures  
- Focal neurologic findings  
- May have associated vesicles and ulcers  
- May have disseminated disease involving multiple organs  
Keratitis, conjunctivitis, retinitis | CSF: elevated WBCs, RBCs present, elevated protein, normal glucose, HSV DNA PCR  
CT: early, unremarkable; late, low-density contrast-enhancing lesions in temporal area, mass effect, edema, and hemorrhage |
| Progressive multifocal leukoencephalopathy | Subacute onset  
- Weakness, hemiparesis  
- Cognitive impairment  
- Speech impairment  
- Vision impairment  
- Ataxia  
- Sensory abnormalities | CT: multiple radiolucent areas in white matter without edema, mass effect, or contrast enhancement  
CSF PCR for JC virus |

CSF, cerebrospinal fluid; WBCs, white blood cells; LP, lumbar puncture; AFB, acid-fast bacilli; TB, tuberculosis, CXR, chest x-ray; IgG, immunoglobulin G; PMN, polymorphonuclear leukocytes (neutrophils); PCR, polymerase chain reaction; HSV, herpes simplex virus; RBCs, red blood cells.

### Table 4. Treatment of secondary CNS infections in children with HIV

<table>
<thead>
<tr>
<th>Infection</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Bacterial meningitis | Neonates >2000 g:  
- Ampicillin IV  
If age <7 days, 200 mg/kg/day ÷ q 12 h  
If age >7 days, 300 mg/kg/day ÷ q 8 h and  
- Gentamicin IV  
If age <7 days, 2.5 mg/kg/dose q 12 h  
If age >7 days, 2.5 mg/kg/dose q 8 h and  
- Cefotaxime 100-180 mg/kg/day ÷ q 6 h IV  
Infants and children:  
- Chloramphenicol 100 mg/kg/day ÷ q 6 h IM/IV and  
- Ampicillin 200 mg/kg/day ÷ q 6 h IM/IV or  
- Benzylpenicillin 240 mg/kg/day (400,000 U/kg/day) ÷ q 6 h IM/IV  
Consider dexamethasone 0.6 mg/kg/day ÷ q 6 h for 2 days (initiate before or with first dose of antibiotics) |

Continued on next page
Table 4. Treatment of secondary CNS infections in children with HIV (continued)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| **Mycobacterium tuberculosis**  | **Initial phase:** 2 mo  
  • Isoniazid 10-15 mg/kg PO daily  
  • Rifampicin 10-20 mg/kg PO daily  
  • Pyrazinamide 20-30 mg/kg PO daily, and  
  • Streptomycin 20-40 mg/kg IM daily  
  Prednisone 2 mg/kg daily, up to 4 mg/kg daily for the most seriously ill, for 4 weeks; then tapered over 1-2 weeks  
  **Continuation phase:** 4 mo  
  • Isoniazid 10-15 mg/kg PO daily  
  • Rifampicin 10-20 mg/kg PO daily |
| **Cryptococcal meningitis**     | **Induction:** ≥14 days (until CSF culture negative)  
  • Amphotericin B 1 mg/kg/day IV infusion  
  (Note: adequate hydration must be maintained during amphotericin amphotericin infusion)  
  **Consolidation:** ≥8 weeks  
  • Fluconazole 12-15 mg/kg daily  
  **Secondary prophylaxis:**  
  • Fluconazole 6-10 mg/kg daily until:  
    – Asymptomatic with last episode of Cryptococcus >12 months ago  
    – If age >6 years old, CD4 >200 cells/µL, if age 2-6 years old, CD4% >25% (Do not stop secondary prophylaxis when age <2 years.)  
  *Management of increased intracranial pressure by daily lumbar punctures. Lumbar punctures to control increased intracranial pressure are essential to successful treatment.* |
| **Toxoplasma encephalitis**     | • Pyrimethamine 2 mg/kg/day ÷ q 12 h for 3 days, then 1 mg/kg/day ÷ q 12-24 h for 4 weeks and  
  • Sulfadiazine 100-200 mg/kg/day ÷ q 6 h for 3-4 weeks and  
  • Leucovorin (folinic acid)  
  **Alternatives:**  
  High-dose TMP/SMX or pyrimethamine and clindamycin  
  Corticosteroids appear useful in ocular or CNS disease  
  Lifelong TMP/SMX prophylaxis |
| **CMV retinitis**               | **Intraocular ganciclovir**  
  Alternative: IV ganciclovir 10 mg/kg/day ÷ q 12 h IV for 14 days; followed by 5 mg/kg/day indefinitely or oral valganciclovir |
| **HSV encephalitis**            | Acyclovir 1500 mg/m²/day ÷ q 8 h IV or 30 mg/kg/day ÷ q 8 h IV  
  **Total course:** 21 days |
| **Progressive multifocal leukoencephalopathy** | **HAART** |

IV, intravenous; IM, intramuscular; PO, per os (by mouth); TMP/SMX, trimethoprim-sulfamethoxazole (Bactrim or cotrimoxazole)
levels. Evidence of myopathic changes can also be seen on electromyogram. Myopathies in HIV-infected patients may also be related to the use of corticosteroids or statin drugs (used to treat lipid disorders) or to hypothyroidism. Treatment involves addressing the causative agent.

**HIV Myelopathy**

Myelopathy is characterized by functional disturbance or pathologic changes in the spinal cord. Progressive difficulty walking and weakness in the lower extremities may be observed. The patient may develop sensory disturbances and urinary incontinence. As with myopathy, myelopathy is more commonly seen in HIV-infected adults than in children. Myelopathy may result from a reactivated infection with measles or CMV. The primary treatment for HIV-related myelopathy is antiretroviral therapy. Myelopathies may also be related to spinal cord tumors and epidural abscesses. These etiologies should be ruled out as part of the diagnosis and management of HIV-infected children with myelopathy.

**Peripheral Neuropathy**

There are many causes of peripheral neuropathy in children with HIV infection. Common etiologies include viral pathogens (including HIV itself), autoimmune effects, vitamin and mineral deficiencies, and side effects of drugs. The symptoms of peripheral neuropathy range from mild numbness or tingling to debilitating pain. Early peripheral neuropathy is often characterized by symmetric numbness and tingling of the extremities in a “stocking glove” distribution. Later stages may be characterized by paresthesias, pain (commonly burning pain that is worse at night), increased sensitivity to touch, diminished reflexes, and weakness. Children may not be able to describe their symptoms well. Thus, one must consider peripheral neuropathy as a possible cause of apparent pain or decreased activity in young children.

HIV can cause peripheral neuropathy by generating a tissue-specific autoimmune attack on peripheral nerves. Varicella-zoster virus causes symptoms along a sensory dermatome (shingles) more commonly in immunosuppressed patients. CMV-related polyradiculoneuropathy (inflammation of the nerve roots) also leads to peripheral neuropathy. HIV-infected children sometimes develop peripheral neuropathies related to vitamin B12 or pyridoxine deficiency. Certain antiretroviral nucleoside analogues (ddC, ddI, d4T) are neurotoxic and may exacerbate or trigger peripheral neuropathy. HIV-infected patients may be on other drugs such as isoniazid that can precipitate peripheral neuropathy. When a patient is suspected of having peripheral neuropathy, the provider should take a careful history to determine likely contributing factors.

Discontinuing drugs known to contribute to peripheral neuropathy often allows improvements in the patient’s condition. Several supplements and medications are also used to help improve symptoms. Some relatively low-cost options include B vitamins, folate, amitriptyline, and topical capsaicin.

**Sleep Problems**

Both quality and quantity of sleep are important to normal growth, development, and health of children. Sleep disturbances occur more commonly among HIV-
infected children and adults than among noninfected individuals. Sleep disturbances occur early in the course of HIV infection. HIV is thought to affect sleep via several mechanisms. Animal studies have suggested that HIV gp120 protein directly alters sleep architecture. Interleukin 1, which is considered a somnogenic lymphokine, is also produced in higher levels with HIV infection. Other medical problems, poor diet, and some medicines can also affect sleep in patients with HIV.

Patients taking efavirenz often report an increase in recollection of dreams and morning sluggishness. Sleep studies have shown that after the initiation of efavirenz, patients spend different amounts of time in various sleep stages such as REM (rapid eye movement) sleep. In most patients, these changes diminish over time and patients rarely report persistent sleep problems after a few months on efavirenz. In rare cases, the sleep problems are more severe and persistent, requiring a medication switch. For children on efavirenz, there must be a high index of suspicion for sleep problems. Children and their caregivers will rarely report such problems without direct questioning. When evaluating these patients, clinicians should ask about changes in daily activity levels (either decreased energy or hyperactivity), school performance in older children, and nightmares or nocturnal awakenings.

Problems other than poor sleep that should be considered in excessively fatigued patients with HIV include poor diet, anemia, hypothyroidism, inactivity, anxiety, and depression. Lifestyle changes including improving diet, getting regular exercise, and reducing stress can often have a profound effect on lessening fatigue.

**Psychiatric Manifestations of HIV in Children**

The World Health Organization estimates that one in four people presenting for health care has a mental health problem. Most of these conditions remain undiagnosed and untreated. Patients with HIV are at increased risk of several mental health problems. These conditions often profoundly affect quality of life. Psychiatric problems also lead to increased stigmatization and present significant challenges to medication adherence. In low-resource settings, specialized medical professionals are usually not available to perform comprehensive psychiatric evaluations. Treatments for psychiatric problems may also be limited. Health professionals in all settings, however, must screen for psychiatric problems so that they can provide the highest standard of care and support available.

Mental health problems that are seen more commonly in children with HIV include depression, delirium, anxiety disorders including posttraumatic stress disorder, attention deficit-hyperactivity disorder, and substance abuse problems. HIV-infected patients are at increased risk of mental health problems caused by the effects of HIV on the brain, the effects of secondary infections on the CNS, metabolic abnormalities, vitamin deficiencies, and side effects of medications used to treat HIV. Life stresses associated with HIV infection may also worsen mental health problems. Asking questions about signs and symptoms that are commonly associated with mental health problems can help identify children who are suffering from these difficulties.

Many case studies involving patients with late-stage HIV infection have documented psychotic and mood symptoms. The cause of the psychiatric symptoms is usually not clearly defined in such cases. In some patients, however, symptoms have improved when antiretroviral therapy was initiated. However, although antiretroviral medications often have a beneficial effect on psychiatric symptoms in late-stage HIV patients, the antiretroviral medicines themselves can also cause psychiatric symptoms. Efavirenz, in particular, has been associated with several adverse psychiatric side effects. Many patients who initiate efavirenz develop neuropsychiatric side effects, including depressed mood, sleep disturbances, anxiety, psychosis, impaired concentration, vivid dreams, and nightmares. Warning patients and family members that these side effects may occur is important. The problems usually resolve after a few weeks or months on efavirenz and discontinuation is usually not necessary.

In HIV-infected patients, depressed mood is rarely, if ever, due to direct effects of HIV on the brain. Therefore, the etiology of the mood symptoms should be intensely sought in patients with HIV and depression. Vitamin B12 and folate deficiencies have been associated with depression. Patients with HIV infection have an increased risk of vitamin B12 deficiency caused by malabsorption and altered metabolism. Thyroid dysfunction, another common contributor to depression, has been seen at an increased rate among HIV-infected children. These
conditions should be ruled out in patients presenting with depressive symptoms.

The evaluation of patients with HIV infection and psychiatric disorders should always include a full medical evaluation. When identified, contributors to psychiatric problems should always be addressed. Psychotropic medications should also be used in HIV-infected patients, including children, to help control symptoms. Patients with HIV may be treated with the same psychotropic medications that have proven to be effective in noninfected patients. Dosing may have to be altered, however, because of the presence of interactions between certain psychotropic and antiretroviral medications.

**References**