A healthy 24-year-old man presented with 1 week of headache, gait imbalance, and coordination difficulties. His mother reported that he had experienced personality changes. He denied any fevers, chills, night sweats, or weight loss. He reported smoking marijuana and denied tobacco and intravenous drug use. He is sexually active, with multiple male partners.

On examination, he was alert and oriented, with a temperature of 36.3°C, blood pressure of 131/90 mm Hg, heart rate of 94/min, respiratory rate of 18/min with pulse oximetry of 98% on ambient air, and a body mass index of 28.1 (calculated as weight in kilograms divided by height in meters squared). Neurologic examination was significant for hyperreflexia in all extremities, bilateral shoulder weakness, and right-sided pronator drift. Laboratory results showed a white blood cell count of 3600/μL (73.5% neutrophils, 16.4% lymphocytes, 7.8% monocytes, 1.4% eosinophils, 0.6% basophils); the remainder of the complete blood cell count and comprehensive metabolic profile was unremarkable. The result of a human immunodeficiency virus (HIV) type 1 antibody test was positive, and CD4 cell count was 73/mm³. Results of serologic testing for Toxoplasma gondii IgG were negative. Computed tomography (CT) imaging of the brain showed a left caudate nucleus and lentiform nucleus lesion with mass effect on the left lateral ventricle (Figure, left panel). Fluid-attenuated inversion recovery magnetic resonance imaging (MRI) of the brain confirmed the presence of an aggressive mass lesion extending through the corpus callosum (Figure, right panel). CT of the chest, abdomen, and pelvis and spinal MRI were unremarkable.

**WHAT WOULD YOU DO NEXT?**

A. Begin antiretroviral therapy (ART)
B. Obtain a brain biopsy
C. Perform a lumbar puncture for examination of cerebrospinal fluid (CSF)
D. Start treatment for central nervous system (CNS) toxoplasmosis
Diagnosis
Primary CNS lymphoma (PCNSL)

What to Do Next?
B. Obtain a brain biopsy

The key to the diagnosis in this case was an imaging finding of an aggressive solitary lesion suggesting malignancy. The most common malignant brain mass in patients with AIDS is PCNSL, particularly in individuals with CD4 cell counts less than 100/mm³. Brain tumors arising from CNS tissue and metastatic malignancies are possible but less likely. Since PCNSL is an Epstein-Barr virus (EBV)-associated B-cell lymphoma, a positive toxoplasma polymerase chain reaction (PCR) assay is highly suggestive of the diagnosis. In this case, a lumbar puncture (option C) was contraindicated because of imaging consistent with increased intracranial pressure. Other causes of brain mass in patients with human immunodeficiency virus (HIV) are toxoplasma encephalitis and progressive multifocal leukoencephalopathy. The latter does not manifest with a mass effect as seen in this case, but toxoplasma encephalitis can present as a solitary, aggressive mass on MRI. This patient had a negative toxoplasma IgG serologic status, making toxoplasmosis unlikely. Had he presented subacutely, multiple ring-enhancing lesions on MRI, and/or had a positive toxoplasma serologic status, a treatment trial with 10-14 days of sulfadiazine and pyrimethamine for toxoplasmosis would be reasonable before considering a brain biopsy (option D). However, the rapid progression, lack of above-mentioned features, and possibility of PCNSL required more urgent diagnosis and treatment. Antiretroviral therapy (ART) is clearly indicated and was given to the patient (option A); outcomes with PCNSL improve when the viral load declines and CD4 cells recover. However, confirming the diagnosis (option B) is vital before initiating antitumor therapy.

Discussion
Prior to the ART era, non-Hodgkin lymphoma (NHL) was more than 100 times more common in HIV-infected individuals compared with non–HIV-infected individuals. With the advent of ART, this ratio dropped 8- to 10-fold. The most common HIV-associated NHL is diffuse large B-cell lymphoma, followed by other NHL types, Burkitt lymphoma and PCNSL, in descending frequency of occurrence. The 5-year survival rate for these HIV malignancies also declines in the same order, from diffuse large B-cell lymphoma (44%) to PCNSL (23%).

To identify the cause of a mass lesion in patients with HIV, imaging findings (location, enhancement, multiplicity), CD4 cell count, serologic status for toxoplasma, and use of sulfamethoxazole-trimethoprim for Pneumocystis jiroveci prophylaxis can help predict the etiology of brain lesions. On CT and MRI, this patient had a single, enhancing periventricular lesion, all characteristic features of PCNSL. The corpus callosum and basal ganglia are the most common locations for PCNSL. PCR assay of the CSF for EBV is a marker of HIV-associated PCNSL. Using a relatively high cutoff (>10 000 copies/mL), PCR has a specificity of 96% and a positive predictive value of 50%; however, there is no consensus about whether this test is predictive enough to permit treatment for PCNSL without a confirmatory biopsy. Thallium-201 scanning is another diagnostic method for PCNSL (sensitivity, 77%; specificity, 81%), as reported in a study of 68 symptomatic patients with HIV and focal brain lesions. Diagnostic accuracy was increased to 100% in a subset of 13 patients who had both thallium scanning and CSF PCR for EBV with concordant results.

Brain biopsy is the gold standard for diagnosis; however, it is not without mortality and morbidity (0.92% and 5.7%, respectively, in a large meta-analysis). Treatment of presumed PCNSL without tissue diagnosis remains controversial. There are no guidelines for when to perform a biopsy, but several algorithms have been suggested.

Whole-brain radiation has been the mainstay treatment for PCNSL, but because of potential neurotoxicity, this therapy has been supplanted by high-dose methotrexate, often in combination other chemotherapeutic agents, immunotherapy with rituximab or both. Rituximab is not established protocol, but nonrandomized studies suggest benefit early in therapy when the damaged blood-brain barrier is permeable to antibodies. Combinations with rituximab are nonstandard and best administered in the context of a research study.

Patient Outcome
The patient received high-dose methotrexate and rituximab followed by delayed whole-brain radiation. He had excellent response to ART; however, his treatment was frequently interrupted because of infections. His neurologic condition worsened, and he died 6 months later.