# Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

# Progressive Multifocal Leukoencephalopathy/JC Virus Infection

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## Epidemiology

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system (CNS), caused by the polyoma virus JC virus (JCV) and characterized by focal demyelination.[1,2] The virus has worldwide distribution, with a seroprevalence of 39% to 69% among adults.[3-6] Primary JCV infection usually occurs asymptomatically in childhood resulting in a chronic asymptomatic carrier state in most individuals. Viral DNA is detected in 20% to 30% of immunoliogically normal adults' urine.[4,7-11]

Outside the context of HIV infection, PML is rare and characteristically manifests as a complication of other immunocompromising diseases or therapies.[12-14] In recent years, PML has been reported in patients treated with immunomodulatory humanized antibodies, including natalizumab,[15] efalizumab,[16,17] and rituximab.[18] Concern has been raised about a possible increased risk of PML in HIV-infected patients treated with rituximab for non-Hodgkin lymphoma,[19,20] but no reports have yet documented PML in that setting. Chronic immunosuppression after organ transplantation is occasionally complicated by PML with a very guarded prognosis.[21]

Before the advent of combination antiretroviral therapy (ART), PML developed in 3% to 7% of patients with AIDS[22-24] and was almost invariably fatal; spontaneous remissions were rare.[25] With the widespread use of ART in the developed world, incidence of PML has decreased substantially,[26,27] and mortality in HIV-infected persons who develop the disease has declined.[28,29] Although most CNS opportunistic infections are almost wholly prevented when CD4 T-lymphocyte (CD4 cell) counts are maintained above 100 to 200 cells/mm$^3$ PML can still sometimes occur in patiens treated effectively with ART.[2,30,31] PML can also develop in the setting of initiating ART and immune reconstitution, discussed below.[2,32]

## Clinical Manifestations

PML manifests as focal neurological deficits, usually with insidious onset and steady progression. Because the demyelinating lesions can involve different brain regions, specific deficits vary from patient to patient. Any region of the CNS can be involved, although some areas seem to be more favored, including the occipital lobes (with hemianopsia), frontal and parietal lobes (aphasia, hemiparesis, and hemisensory deficits), and cerebellar peduncles and deep white matter (dysmetria and ataxia).[12] Spinal cord involvement is rare and the optic nerves are not involved.[33] Although lesions can be multiple, one is often clinically predominant. Initial symptoms and signs usually begin as partial deficits (e.g., weakness in one leg) that worsen over time and involve a larger territory (e.g., evolution to hemiparesis) as individual lesions expand concentrically or along white matter tracts. The focal or multifocal nature of the pathology is responsible for the consistency of clinical presentations with distinct focal symptoms and signs, rather than as a more diffuse encephalopathy, or isolated dementia or behavioral syndrome, all of which are uncommon without concomitant focal findings.[34]

The time course of this evolving demyelination, with clinical progression over several weeks, often provides a clue to diagnosis because the other major opportunistic focal brain disorders (cerebral toxoplasmosis and primary CNS lymphoma) characteristically progress in hours to days and cerebral infarcts begin even more abruptly. Nonetheless, PML is sometimes mistaken for an evolving stroke, which like PML is bright on diffusion weighted MRI. While rather sudden onset of a focal brain lesion can mimic strokes, the gradually progressive course should rapidly make this diagnosis unlikely with subsequent diagnostic evaluations undertaken to identify PML. Headache and fever are not characteristic of the disease, and when present may indicate presence of another opportunistic infection. Seizures develop in nearly 20% of PML patients and are associated with lesions immediately adjacent to the cortex.[35,36]

## Diagnosis

Initial recognition of PML relies on a combination of clinical and neuroimaging findings: steady progression of focal neurological deficits with magnetic resonance imaging (MRI) almost always demonstrating distinct white matter lesions in areas of the brain corresponding to the clinical deficits. The lesions are hyperintense (white) on T2-weighted and fluid attenuated inversion recovery sequences and hypointense (dark) on T1-weighted sequences.[2] The T1 findings can be subtle and help distinguish lesions due to PML from other pathologies, including the white matter lesions of HIV encephalitis. In contrast to cerebral toxoplasmosis and primary CNS lymphoma, no mass effect or displacement of normal structures is usually evident. Although contrast enhancement is present in 10% to 15% of cases, it is usually sparse with a thin or reticulated appearance adjacent to the edge of the lesions. Exceptions to these characteristic imaging findings can occur when the inflammatory form of PML develops in the setting of immune reconstitution after initiation of ART (see below). Advanced neuroimaging techniques, such as diffusion-weighted imaging and magenetic resonance (MR) spectroscopy, may provide additional diagnostic information.[37-39] New PML lesions and the advancing edge of large lesions have high signal on diffusion-weighted imaging and normal-to-low apparent diffusion coefficient signifying restricted diffusion. These changes relate to regions of active infection and oligodendrocyte swelling. MR spectroscopy can show areas of decreased N-acetylaspartate and increased choline related to axonal loss and cell membrane and myelin breakdown, respectively, with the greatest changes at the center of lesions.[40] Recently, a hyperintense cortical signal seen on MRI scan in non-enhanced T1-weighted cortex images has been associated with seizures complicating inflammatory PML.[36]

In most cases of PML, the combined clinical and radiographic presentations support a presumptive diagnosis. Confirming the diagnosis, however, is invaluable. Certainly for atypical cases but even for typical cases, confirmation allows physicians to initiate ART rapidly and with certainty and prevents the need to revisit the diagnosis when disease progression continues. Confirmed diagnosis also informs discussions of prognosis.

The usual first step in confirming the diagnosis is to test cerebrospinal fluid (CSF) by polymerase chain reaction (PCR) for the presence of JCV DNA. The assay is positive in approximately 70% to 90% of patients not taking ART, for whom a positive result can be considered diagnostic in the appropriate clinical context, namely, subacute onset of focal neurological abnormalities and suggestive imaging findings.[9,41] JCV may be detectable in the CSF of as few as 60% of ART-treated patients.[42] In patients not taking ART, the number of JCV DNA copies can add additional information for prognosis, although the relationship between copy number and prognosis is less clear in patients taking ART.[43,44] CSF analysis can be repeated if JCV PCR is negative yet suspicion of PML remains high and alternative diagnoses have been excluded (e.g., by PCR analyses of CSF for varicella zoster virus and Epstein-Barr virus for varicella zoster virus encephalitis and primary CNS lymphoma, respectively). Because JCV DNA viral load in CSF may be very low even with active PML, highly sensitive PCR performance is desirable. Sensitive assays that detect as few as 50 copies/ml are now available, with some research labs exceeding this level of sensitivity., detection of JCV virus in CSF in any amount with the appropriate clinical and imaging findings strongly supports the diagnosis of PML.[45]

In some instances, brain biopsy is required to establish the diagnosis. PML can usually be identified by the characteristic tissue cytopathology, including oligodendrocytes with intranuclear inclusions, bizarre astrocytes, and lipid-laden macrophages, with identification of JCV or cross reacting polyoma virus by immunohistochemistry, in situ nucleic acid hybridization, or electron microscopy.[12,46,47]

Serologic testing is generally not useful because of high anti-JCV seroprevalence in the general population. Recently, however, antibody testing has been assessed for stratifying risk of PML with natalizumab treatment.[6] Significant increases in JC virus specific antibody titers[48] and detection of intrathecally produced anti-JCV antibodies may prove useful for diagnostic testing[49] but requires further prospective study.

## Preventing Exposure

JCV has a worldwide distribution and, as previously noted, 20% to 60% of people exhibit serologic evidence of exposure by their late teens.[50] Currently, there is no known way to prevent exposure to the virus.

## Preventing Disease

In many individuals, JCV infection is likely latent and intermittently productive, although clinically silent, in the kidney or other systemic sites. Systemic infection may increase in the presence of immunosuppression. It remains a subject of debate whether JCV infection is also latent in the CNS or whether PML results from hematogenous dissemination of infection to the brain resulting in subsequent PML lesion development within months of entry to CNS.[51,52] Protection is conferred by either preventing spread to the CNS or by preventing active viral replication with effective immunosurveillance. Therefore, the only effective way to prevent disease is to prevent progression of HIV-related immunosuppression with ART **(AII)**.

## Treating Disease

No specific therapy exists for JCV infection or PML. The main approach to treatment involves ART to reverse the immunosuppression that interferes with the normal host response to this virus. In patients with PML who are not on therapy, ART should be started immediately **(AII)**. In this setting, more than half of HIV-infected PML patients experience a remission in which disease progression stops. Neurological deficits often persist, but some patients experience clinical improvement.[28,29,53-58] In one retrospective study of 118 consecutive patients with PML who received ART, 75 patients (63.6%) survived for a median of 114 weeks (2.2 years) after diagnosis of PML.[58] Neurological function in the survivors was categorized as cure or improvement in 33, stabilization or worsening in 40, and unknown in 2. Another retrospective case series reported that 42% of PML survivors on ART had moderate-to-severe disability.[59] Peripheral blood CD4 cell count at presentation was the only variable that predicted survival; the odds ratio for death was 2.7 among patients with CD4 counts <100 cells/mm$^3$ compared with patients who had higher CD4 cell counts. In other case series, worse prognosis was also associated with high plasma HIV RNA levels at the time of presentation, poor virologic responses to ART, and the presence of lesions in the brain stem.[29,31,54,55,57,58,60] Contrast enhancement on imaging may predict better outcome, as it is indicative of an immune response to the virus.[30] In PML occurring in multiple sclerosis patients, younger age, more restricted unilobar disease, and lower CSF JCV DNA copy numbers are associated with better outcomes.[61]

ART should be optimized for HIV virologic suppression in patients with PML who have received ART but remain viremic because of inadequate adherence or ARV resistance **(AIII)**. More problematic are patients who develop PML despite successful HIV virologic suppression while taking ART. A preliminary report of PML patients treated intensively with four classes of ART (including enfuvirtide) suggested that the strategy might offer higher than anticipated survival,[62] but it has not yet been followed by a full report or structured trial. Therefore, there is no evidence supporting ART intensification for PML.

The use of ARV drugs that better penetrate the CNS also has been proposed, with use of the CNS Penetration Effectiveness (CPE) score of drug regimens as a guide. This score is based on the pharmacology of ARV drugs with respect to their chemical characteristics as well as demonstrated entry into the CNS (or, more often, the CSF) and, where available, on their CNS anti-HIV activity.[63] One report found that at the beginning of the combination ART era, a high CPE score was associated with longer survival after a PML diagnosis, whereas in the late, more recent ART period, the effect of the CPE score disappeared as more potent ARV regimens led to more effective plasma viral load control.[64] Hence, in the current era, the effectiveness of selecting a treatment regimen with a high CPE score is not established. It seems likely that systemic rather than CNS efficacy is the salient aspect of ART in this setting because ART's most important effect on PML may be restoration of effective anti-JCV immunity that can limit CNS infection.[65,66]

The history of more specifically targeted treatments for PML includes many anecdotal reports of success that have not been confirmed by controlled studies. Based on case reports and demonstration of *in vitro* inhibitory activity against JCV, intravenous (IV) and intrathecal cytarabine (cytosine arabinoside) were tested in a clinical trial, but neither demonstrated clinical benefit.[67] Therefore, treatment with cytarabine **is not recommended (AII)**. Similarly, cidofovir initially was reported to have a salutary clinical effect, but several large studies—including retrospective case-control studies, an open-label clinical trial, and a meta-

analysis that included patients from five large studies—demonstrated no benefit.[42,56-58,68] Thus, treatment with cidofovir is also **not recommended (AII)**. A lipid-ester derivative, hexadecyloxypropyl-cidofovir, recently has been reported to suppress JCV replication in cell culture,[69] but its efficacy in HIV-associated PML is unknown.

On the basis of a report indicating that the serotonergic 5HT2a receptor can serve as a cellular receptor for JCV in a glial cell culture system,[70,71] drugs that block the 5HT2a receptor, including olanzapine, zisprasidone, mirtazapine, cyproheptadine, and risperidone, have been suggested as treatment for PML,[72] although the rationale for this practice has been questioned.[73] Again, anecdotes about favorable outcomes[1,74-77] have not been substantiated by reports of genuine benefit in larger case series, cohort studies, or formal clinical trials. Thus, at this time, treatment with this class of drugs **is not recommended (BIII)**.

After a cell-culture study indicated that JCV replication could be inhibited by a topoisomerase inhibitor,[78] an analogue, topotecan, was studied in a small trial. Results suggested a salutary effect in some patients, although the outcome likely was little different from the natural course in other patients with AIDS, and the main toxicities were hematologic.[79] At this time, topotecan also **is not recommended (BIII)**.

A Phase I/II clinical trial of the antimalarial drug mefloquine was initiated based on its demonstrated *in vitro* anti-JCV activity. The trial was later halted by the sponsor, because demonstration of efficacy was futile (http://clinicaltrials.gov/ct2/show/NCT00746941).[80] Mefloquine **cannot be recommended**.

Immunomodulatory approaches to the treatment of PML in HIV-infected patients have also been tried, but none has yet been studied in a prospective, controlled clinical trial. Although an initial retrospective analysis suggested that interferon-alpha might improve survival,[81] a subsequent retrospective analysis did not demonstrate benefit beyond that afforded by ART; therefore, interferon-alpha **is not recommended (BIII)**.[82] A single report described failure of interferon-beta treatment of HIV-associated PML[83] and natalizumab-related PML developed in patients given interferon-beta for multiple sclerosis.[15] Case reports have described improvement or recovery in PML-related neurological dysfunction in three patients who were not HIV infected and were treated with IL-2: one with Hodgkin lymphoma treated with autologous Bone Marrow Transplantation, one with low-grade lymphoma and allogeneic stem cell transplantation, and one with myelodysplastic syndrome.[84-86] Like the other reports, these too have not been followed up with more substantial trials. Recent interest in recombinant IL-7 for treatment of PML when CD4 lymphopenia is persistent, sometimes in combination with VP-1 vaccination strategy, are under consideration as an alternative adjuvant immune therapy to improve PML outcomes.[87-91]

## *Special Considerations with Regard to Starting ART*

ART should be started in patients not on HIV treatment as soon as PML is recognized **(AII)**. For patients already on treatment who have demonstrated plasma HIV viremia and are adherent to therapy, ART should be adjusted based on plasma virus susceptibility **(AII)**.

## *Monitoring of Response to Therapy and Adverse Events (Including IRIS)*

Treatment response should be monitored with clinical examination and MRI. In patients with detectable JCV DNA in their CSF before initiation of ARV treatment, quantitation of CSF JCV DNA may prove useful as an index to follow for assessing treatment response. No clear guidelines exist for the timing of follow-up assessments, but it is reasonable to be guided by clinical progress. Often clinical deterioration is seen before stabilization and improvement occurs.[92] In patients who appear stable or improved, neuroimaging can be obtained 6 to 8 weeks after ART initiation to screen for radiographic signs of progression or of immune response, and can serve as a further baseline for subsequent scans should the patient begin to deteriorate. In patients who clinically worsen before or after this 6- to 8-week period, repeat neuroimaging should be obtained as soon as worsening is recognized **(BIII)**.

### *PML-Immune Reconstitution Inflammatory Syndrome*

PML has been reported to occur within the first weeks to months after initiating ART[2,31,32,93-95] with clinical and radiographic features that differ from classical PML, including lesions with contrast enhancement, edema and mass effect, and a more rapid clinical course.[96,97] As with other presentations of IRIS, it is more likely after advanced HIV with low CD4 counts, and with greater decline in HIV viral load on initiation of ARV. This presentation has been referred to as inflammatory PML or PML-immune reconstitution inflammatory syndrome (PML-IRIS). Both unmasking of cryptic PML and paradoxical worsening in a patient with an established PML diagnosis have been observed. Histopathology typically demonstrates perivascular mononuclear inflammatory infiltration.[98-101] Unmasked PML-IRIS is presumed to represent the effects of a restored immune response to JCV infection in the context of ART, with resultant local immune and inflammatory responses, but other undefined factors also may contribute to unmasked PML-IRIS.

Because ART-induced immune reconstitution may be associated with both onset and paradoxical worsening of PML, corticosteroids have been used empirically in this setting, with reported benefit.[2,94] Further study of corticosteroids for treatment of PML-IRIS is needed to confirm efficacy and refine dosage and duration. At present, however, use of corticosteroids to treat of PML-IRIS appears justified characterized by contrast enhancement, edema or mass effect, and clinical deterioration **(BIII)**. The decision to use steroids can be difficult because it is the immune response to JCV that controls the infection and treatments that blunt that response can be deleterious. Nevertheless, the inflammatory response against PML can, at times, be more damaging than the virus itself, and corticosteroids appear to have a role in treatment of these patients.

The dosage and duration of corticosteroids for PML-IRIS have not been established. In the absence of comparative data, adjuvant corticosteroid therapy should be tailored to individual patients. One approach, modeled on treatment of multiple sclerosis flairs, is to begin with a 3- to 5 day course of IV methylprednisolone dosed at 1 g per day, followed by an oral prednisone taper, dosed according to clinical response. A taper may begin with a dose of 60 mg per day in a single dose, tapered over 1 to 6 weeks. Clinical status should be monitored carefully during this taper in an attempt to minimize systemic and immune effects while avoiding IRIS recrudescence. Contrast-enhanced MRI at 2 to 6 weeks may be helpful in documenting resolution of inflammation and edema and to obtain a new baseline, recognizing that the MRI appearance may worsen despite clinical improvement and that clinical status is likely the best indicator of treatment efficacy. Importantly, ART should be continued at the standard therapeutic doses during this period **(AIII)**.

Several case reports suggest that maraviroc might be beneficial for PML-IRIS,[102] presumably related to the immunomodulatory rather than ARV properties of the CCR5 inhibitor. However, no comparative studies in HIV-associated PML have confirmed benefit of inclusion of maraviroc in HIV therapy in this setting.[102-105]

Although some clinicians may want to use adjuvant corticosteroid therapy to treat all cases of PML regardless of whether there is evidence of IRIS, this action is not justified and should be discouraged in patients who have no evidence of substantial inflammation on contrast-enhanced neuroimaging or on pathological examination **(CIII)**. In patients whose condition worsens, imaging can be repeated to monitor for development of IRIS before initiating corticosteroids.

### *Managing Treatment Failure*

PML remission can take several weeks and there are no strict criteria to define treatment failure. However, a working definition may be continued clinical worsening and continued detection of CSF JCV without substantial decrease within 3 months of initiating of ART. Changes in plasma HIV RNA levels and blood CD4 cell count responses provide ancillary predictive information. Failing ART regimens should be changed based on standard guidelines for the use of ART. When PML continues to worsen despite fully suppressive anti-HIV treatment, one of the unproven therapies described above can be considered, although the possibility of toxicity must be balanced against the unproven benefits of these treatments.

## Preventing Recurrence

Patients who experience remission of PML after ART rarely suffer subsequent recrudescence.[56,106] The main preventive measure, based on its role in reversing the disease, is treatment with an effective ART regimen that suppresses viremia and maintains CD4 cell counts **(AII)**.

## Special Considerations During Pregnancy

Diagnostic evaluation of PML should be the same in pregnant women as in women who are not pregnant. Therapy during pregnancy should consist of initiating or optimizing the ARV regimen. If corticosteroid therapy is initiated during pregnancy, blood sugar monitoring should be included as insulin resistance is increased during pregnancy.

### Recommendations for Preventing and Treating PML and JCV

- There is no effective antiviral therapy for preventing or treating JCV infections or PML.
- The main approach to treatment is to preserve immune function and reverse HIV-associated immunosuppression with effective ART.
- HIV-associated PML is often complicated by clinically significant IRIS that may require administration of corticosteroid therapy **(BII)**.
- In ART-naive patients who are diagnosed with PML, ART should be started immediately **(AII)**.
- In patients who are receiving ART but remain viremic because of inadequate adherence or drug resistance, ART should be optimized to achieve HIV suppression **(AIII)**.

**Key to Acronyms:** ART = antiretroviral therapy; JCV = JC virus; PML = progressive multifocal leukoencephalopathy.

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