# PROGRESSIVE MULTI-FOCAL LEUKOENCEPHALOPATHY

learn about the symptoms, diagnosing and treating this relatively rare brain condition associated with aids

A PUBLICATION FROM
PROJECT inform
Information, Inspiration and Advocacy for People Living With HIV/AIDS

JUNE 2007

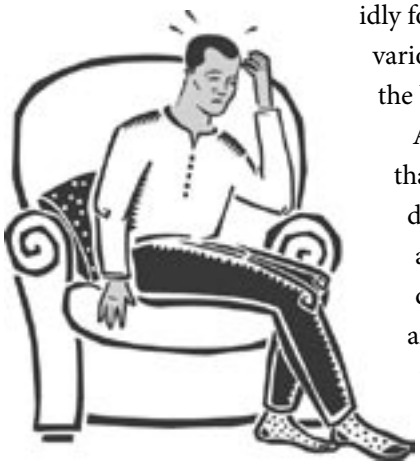

PML is a rare AIDS-related condition of the brain, caused by the JC virus. World wide, more than 4 in 5 adults are exposed to this virus, but it only causes disease in people with weakened immune systems. Before AIDS, PML was rarely seen except in people with advanced cancer or bone marrow transplants.

Today, most PML cases occur in people living with HIV, mainly in those with advanced disease and very low CD4+ cell counts. However, it occasionally appears in people with CD4+ cell counts up to 500. Overall, about 1 in 20 people with AIDS will develop PML. It is unclear why, if most people with HIV also have the JC virus, the rate of PML remains so low.

Because it is so rare and because it affects the brain (an organ that is difficult to study), its diagnosis and treatment are poorly understood. In 2005 and 2006, several people with inflammatory diseases were treated with immune therapy (such as natalizumab) to block inflammatory cells and developed PML. This led to renewed interest in researching this rare disease. As PML becomes better understood, some debate may begin on changing the name of the condition to *JC Virus Encephalopathy*.

## What are the symptoms?

Symptoms do not occur when a person is first infected with JC virus. However, when it infects the brain and begins to cause disease, the infection rapidly forms lesions. This begins to affect various body functions controlled by the brain and nervous system.



A frightening aspect of PML is that there's no "usual" course of disease. Whatever brain areas that are affected by the JC virus will determine how PML appears in an individual. For example, if the virus strikes the part of the brain that controls sight, vision could be lost. If it strikes the part that controls speech or motor skills, one could lose the ability to talk or walk. There is no predicting where or how the virus will attack, and thus what functions will be impaired.

Early symptoms of PML may include weakness in one side of the body or limbs (sometimes very severe), blurred or loss of vision (possibly on one side), fatigue and/or impairments in learned skills that may range from language impairments (*aphasia*) to memory loss, confusion, disorientation or a loss of balance. Nearly 1 in 5 people with PML disease report having seizures.

Symptoms are similar to those of other HIV-related conditions that affect the brain, including toxoplasmosis (*toxo*), lymphoma of the central nervous system (*CNS lymphoma*), AIDS Dementia Complex (ADC), cryptococcal meningitis, HIV encephalopathy and cytomegalovirus (CMV) and herpes infections of the central nervous system. Therefore, it's important to consult with a specialist, called a neurologist, when these symptoms occur to assure a correct diagnosis.

PML is most often mistaken for toxo. Typically, a doctor may suspect PML if treatments fail for other conditions, like toxo. PML can also occur at the same time as swelling of the brain (*HIV encephalopathy*) and toxo.

## How do you diagnose PML?

Diagnosing PML is tricky. PML, toxoplasmosis, AIDS dementia complex, cryptococccal meningitis and lymphoma, CMV and even herpes virus infections in the brain can appear like one another on an MRI scan, a type of x-ray of the brain. All of these conditions have been associated with HIV. Because the lesions can look similar on an MRI, it's important to continue the diagnosis by doing a brain biopsy. This way the exact cause can be determined and treated properly. A small hole is drilled into the skull and a piece of tissue is removed and examined. If the JC virus is found in the tissue, PML is diagnosed. A brain biopsy is considered the gold standard for diagnosing PML.

Some people who are presumed to have PML will elect not to have a brain biopsy. Doctors, as well as some surgeons, may not recommend it because it is invasive and causes discomfort. Even if a definite diagnosis of PML comes back, no therapies are very effective at treating the condition with the exception of changes in anti-HIV therapy. A doctor and patient may opt to make these changes regardless of a definitive PML diagnosis.

The main benefit of doing a biopsy is to rule out other possible brain diseases that may be more readily treated. If a person decides not to have the biopsy to confirm PML, doctors sometimes still recommend treating these other common brain diseases on the off chance that the condition is treatable.

When the brain biopsy is not done, PML will be diagnosed using three pieces of information. This includes: 1) if the state of health is consistent with PML symptoms; 2) if JC virus DNA is present in the cerebral spinal fluid; and 3) if MRI tests show lesions mainly in the brain's white matter. However, using anti-HIV therapy complicates the choice to do a brain biopsy in diagnosing PML. The lesions may look different, including more inflammation than what's normally seen, when potent anti-HIV therapy is used.

Another form of x-ray called a computed tomographic (CT) scan may show problems in the brain, but it is not as sensitive as an MRI. Testing for antibodies to the JC virus in blood or urine is also not a good way to detect active JC virus. This is because up to 4 in 5 adults already have these antibodies, with or without HIV infection.

## How do you treat PML?

Until recently, a diagnosis of PML was quite grim. The one therapy used for treating it, a toxic drug called cytosine arabinoside (ara-C, cytarabine, Cytosar-Ur), is given through a shunt directly into the brain. It has shown marginal, if any, benefit. It is no longer routinely used, though some feel that new drug delivery systems warrant renewed research.

Before the arrival of potent anti-HIV therapy, the average time from diagnosis of PML to death was 1–3 months. Recent studies show that using aggressive anti-HIV therapy may result in an indefinite remission of PML for some people.

Nearly 1 in 10 people with PML have recovered with or without treatment. Spontaneous recovery or stabilization is more likely to occur in people with CD4+ cell counts above 200. The unpredictable nature of this issue presents a perplexing challenge to doctors treating PML.

## Potent anti-HIV therapy

Several groups have reported symptom-free survival after a PML diagnosis of over ten years and counting for some people using potent anti-HIV therapy. Factors associated with improved survival include using an anti-HIV regimen with a protease inhibitor and changing to a new regimen after a PML diagnosis.

A more recent study shows extremely encouraging results, perhaps the best to date, with "enhanced" anti-HIV therapy. This is when Fuzeon (enfuvirtide, T-20) is added to a traditional regimen with protease inhibitors. At six months, the survival rate was 3 out of 4 people and the trend suggested this survival rate may hold to one year and beyond.

While there are no guidelines for anti-HIV therapy and PML, it would be fair to make a few assumptions based on gathered information. After a presumptive diagnosis of PML is made and whether or not a person elects to have a brain biopsy, it seems advisable to start or change to a new potent anti-HIV regimen including a protease inhibitor. Experienced neurologists who choose to treat PML with anti-HIV drugs once recommended using anti-HIV drugs that penetrate the blood-brain barrier. This included using high doses of AZT daily (1,000–1,200mg) because lower doses are not as effective at crossing this barrier. More recently, however, experts have changed their thinking about the importance of using drugs that cross the blood-brain barrier in a potent anti-HIV regimen when treating PML.

Increasingly they believe that the benefits of anti-HIV therapy are due to better immune responses throughout the body. This supports the notion of creating the most potent possible regimen based on resistance testing, history of anti-HIV drug use, and cross resistance issues. This is supported by the very encouraging results of the "enhanced" therapy study—where adding Fuzeon appears to have a profoundly beneficial effect, but is not believed to cross the blood-brain barrier whatsoever.

## Cytosine arabinoside (Ara-C)

Cytosine arabinoside (ara-C, cytarabine, Cytosar-Ur) is currently used as chemotherapy for leukemia and cancer. For treating PML it was commonly given through a shunt into the brain and/or directly into a vein (intravenously). Experienced neurologists may dose ara-C through a shunt (called intrathecally) into the brain at doses of 10mg/m$^2$ for three days, followed by 10mg/m$^2$ twice a week for two weeks, then 20–30mg/m$^2$ each week thereafter. The common dose of ara-C when given into a vein is 2mg/kg in 5-day cycles, every 15 or 30 days.

Side effects include nausea, consistent fevers and bone marrow toxicity. These effects are dependent on its dose and schedule and vary in severity. Ara-C can harm an unborn child in pregnant women. Checking blood work is necessary, including daily platelet, leukocyte counts and bone marrow exams during treatment. Some doctors give a dose of G-CSF (granulocyte colony stimulating factor, Neupogen) for one week before starting ara-C to relieve bone marrow toxicity. Prednisone may help reduce side affects.

While ara-C was once considered standard-of-care for people with PML who chose treatment, it has fallen out of favor due to its side effects, low success rate and the superior responses seen from using potent anti-HIV therapy.

## Experimental treatments

**CIDOFOVIR:** Several studies of the anti-CMV drug, cidofovir, first looked encouraging for treating PML. However, over time these studies failed to show any benefit and so it is no longer recommended for treating PML.

**CORTICOSTEROIDS:** There is some debate about adding corticosteroids to potent anti-HIV therapy for treating PML. Those opposed to using them say they may further weaken the immune system, which is critical in successfully treating PML. There are also a few cases where the development of PML has been associated with their use. Those in favor of using corticosteroids note that increased inflammation associated with using anti-HIV therapy may be quieted by using these steroids and thus aid PML recovery. Currently, experts are interested in studying corticosteroids as an added therapy to potent anti-HIV therapy for PML.

**INTERFERON THERAPY:** Researchers have been interested in using both Interferon-alpha and Interferon-beta to treat PML. In test tube studies, both are active against the JC virus. However, studies in people with PML have been terribly underwhelming. Researchers feel that if there were better ways to target the therapy to the brain lesions and the virus, it may be worth revisiting the research on these therapies.

**5HT2A ANTAGONISTS:** This includes drugs like Remeron (mirtazapine)—a drug usually used to treat depression—and other similar drugs. Some speculate that this class of drugs might be useful in treating PML. Experts have gathered anecdotal information as they ponder further research. Their first reaction to the anecdotes is that they are not terribly impressive. Even still, when added to anti-HIV therapy, this class may provide a new therapy.

**OTHER POSSIBLE INTERVENTIONS:** for study include interleukin-2 (IL-2), topoisomerase inhibitors (topotecan, camptothecan, etc.), adoptive cell therapy (enhancing JC virus specific cellular immunity) and RNAsi.

## drug i.d. chart

| TRADE NAME | GENERIC NAME |
|---|---|
| **Protease inhibitor** | |
| Agenerase | amprenavir |
| Aptivus | tipranavir |
| Crixivan | indinavir |
| Invirase | saquinavir hgc |
| Kaletra | lopinavir+ritonavir |
| Lexiva | fosamprenavir |
| Norvir | ritonavir |
| Reyataz | atazanavir |
| Viracept | nelfinavir |
| **Nucleoside (NRTI) and nucleotide (NtRTI) analogue reverse transcriptase inhibitor** | |
| Combivir | 3TC+AZT |
| Emtriva | emtricitabine (FTC) |
| Epivir | lamivudine (3TC) |
| Epzicom | 3TC+abacavir |
| Retrovir | zidovudine (AZT) |
| Trizivir | 3TC+AZT+abacavir |
| Truvada | FTC+tenofovir |
| Videx | didanosine (ddI) |
| Videx EC | didanosine enteric-coated (ddI EC) |
| Viread | tenofovir |
| Zerit | stavudine (d4T) |
| Ziagen | abacavir |
| **Non-nucleoside reverse transcriptase inhibitor (NNRTI)** | |
| Rescriptor | delavirdine |
| Sustiva | efavirenz |
| Viramune | nevirapine |
| **NRTI + NNRTI** | |
| Atripla | Emtriva+Sustiva+Viread |
| **Entry inhibitor** | |
| Fuzeon | enfuvirtide (T20) |

**www.projectinform.org**

**Go online around the clock and get connected to treatment information in the privacy of your own home!**

## Commentary

Currently, some doctors assert that PML is not treatable. However, many people have responded to various treatments. Although anti-HIV therapy does not directly affect the JC virus, the wise use of it appears to greatly impact survival after a PML diagnosis, most likely because the immune system recovers and starts to control the JC virus once HIV replication is arrested.

It is important to realize that successful PML treatment at best usually means only stabilizing or partly resolving symptoms, even when brain lesions shrink. This is different from a complete resolution of symptoms. Despite an arrest or decrease of lesions in the brain, someone with PML may face lifelong symptoms. These may include weakness on one side of the body or limbs, loss of vision and/or permanent impairment of certain functions (slurred speech, memory loss, disorientation, loss of balance, etc.), even if survival is extended and PML lesions stabilize or improve.

In one reported case of complete resolution of PML lesions in the brain after starting HAART—despite their loss—partial vision loss caused by the JC virus in the part of the brain that controls sight remained permanent. This suggests that treating PML early and aggressively is wise as the damage that is allowed to continue, unchecked, may be permanent. It is not uncommon, however, after a brain injury or disease for the brain to repair somewhat, or for other parts of the brain to compensate and for symptoms from the condition to improve.

PML is difficult to study. Factors that add to this difficulty include the rapid onset of symptoms, similarities to other conditions like toxo, and the fact that some people spontaneously recover or stabilize for unknown reasons. Most information on PML treatments now comes from small studies and anecdotal reports.

PML diagnosis remains a problem. A brain biopsy is quite invasive and therefore less invasive techniques need to be developed. A spinal tap (*lumbar puncture*) is hardly non-invasive, but compared to a brain biopsy it's a far better choice to many people.

Among people with HIV, about 30% without and 70% with PML have detectable JC virus floating in their blood. Given the large percentage of people with measurable levels of JC virus without PML, using blood as a way to diagnose PML is not practical. Far too many people without PML could be misdiagnosed as having PML. Using cerebral spinal fluid (CSF) to diagnose PML may provide a medium ground, but it's not perfect.



### the bottom line on pml

- **PML is a rare condition affecting the brain, caused by the JC virus.**
- **PML is difficult to diagnose, definitive diagnosis requires a brain biopsy.**
- **JC virus DNA levels in cerebral spinal fluid are prognostic. Higher levels relate to more aggressive disease.**
- **Using potent anti-HIV therapy, including a protease inhibitor, has had a profound positive effect on treating PML.**
- **Using a protease inhibitor after a PML diagnosis, as well as changing to a new anti-HIV regimen with a protease inhibitor, has resulted in quadrupling the survival rates of some people living ten years or more after a PML diagnosis.**
- **A new study shows that "enhanced" anti-HIV therapy, or adding the drug enfuvirtide to a regimen, may be very promising. Whether or not adding newer classes of drugs, like integrase inhibitors, are equally promising has yet to be seen.**