

# Progressive Multifocal Leukoencephalopathy (PML)



## PML

Progressive Multifocal Leukoencephalopathy (PML) is a rare AIDS-related condition of the brain, caused by a virus called the JC virus. Between 80-85% of all adults are exposed to this virus worldwide, but it appears to only cause disease in people with weakened immune systems.

PML was rarely seen before AIDS except in people with advanced cancer or in people who were immune suppressed for purposes of bone marrow transplant.

Today, most PML cases occur in people living with HIV, primarily those in advanced stage disease with very low CD4+ cell counts. However, it can occasionally appear in people with CD4+ cell counts upwards of 500. It's the first AIDS-defining condition diagnosed in about one percent of people with HIV.

It is unclear why, if most people with HIV also have the JC virus, PML doesn't affect more people. Because it's so rare and because it affects the brain—an organ that is difficult to study—its diagnosis and treatment are poorly understood.

### Symptoms

When the JC virus infects the brain, it rapidly forms lesions and begins affecting various functions controlled by the brain and nervous system. PML can be frightening to because there is no "usual" course of disease.

The functions controlled by the area of the brain affected by the JC virus will determine how PML will manifest. For example, if the virus strikes the part of the brain that controls sight, then vision could be lost. If it strikes the part controlling speech or motor skills, one could lose the ability to talk or walk. One cannot predict where or how the virus will attack and 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) and fatigue. They may also include impairments in learned skills ranging from language impairments (called *aphasia*) to memory loss, confusion, disorientation or a loss of balance.

Symptoms of PML are similar to those of other HIV-related conditions that effect the brain. These include toxoplasmosis, lymphoma of the central nervous system (CNS lymphoma), AIDS Dementia Complex (ADC), cryptococcal meningitis and cytomegalovirus (CMV) and herpes infection of the central nervous system. Therefore, when symptoms first appear, consulting a specialist (called a *neurologist*) is important to assure an accurate diagnosis.

PML is most often mistaken for toxoplasmosis. Typically PML may be suspected if treatments for other complications, such as toxoplasmosis, fail. PML can also occur at the same time as HIV swelling of the brain (called HIV *encephalopathy*) and toxoplasmosis.

### Diagnosis

Diagnosing PML is tricky. PML, toxoplasmosis, AIDS Dementia Complex, cryptococcal meningitis, lymphoma, CMV and herpes infections in the brain can look similar 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 MRIs, it's important to pursue diagnosis by a brain biopsy so the cause can be determined and treated properly. For the biopsy, a small hole is drilled into the skull and brain tissue is removed and analyzed. If the tissue contains the JC virus, a diagnosis of PML is made.

Some people who are presumed to have PML will choose not to have the biopsy. Doctors, as well as some surgeons, may be reluctant to recommend the procedure because it is invasive and causes discomfort. And, even though a PML diagnosis may result from the procedure, no therapies are very effective at treating the condition.

The main benefit of a brain biopsy is that it rules out other possible brain diseases that may be more readily treated. If a person chooses not to have a biopsy to diagnose PML, doctors sometimes recommend treatment for other common brain-related conditions, just in case the condition is treatable.

Another form of X-ray, called computed tomographic (CT) scanning, may show abnormalities in the

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brain, but it's not as sensitive as the MRI test. Blood or urine tests for JC virus antibodies in blood or urine are not a good way to detect active JC virus either, since about 80% of adults already have these antibodies, with or without HIV infection. Researchers are also currently investigating polymerase chain reaction (PCR) technology to look for JC virus in spinal fluid. (PCR technology is used to measure HIV levels.)

## Treatment

Before now, a PML diagnosis 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 and has shown marginal, if any, evidence of benefit. A recent study showed that ara-C was not beneficial whatsoever, while earlier studies show conflicting results.

The average time from PML diagnosis to death, before highly active anti-HIV therapy (HAART), was 1-3 months. Recent studies suggest that aggressive anti-HIV therapy may result in an indefinite remission of PML for some people.

About 10% of people with PML have recovered with or without treatment. Spontaneous recovery or stabilization is more likely to occur in people with CD4+ cell counts over 200. And, the unpredictable response to this disease continues to present a perplexing challenge to doctors treating PML.

## Cytosine arabinoside (Ara-C, cytarabine, Cytosar Ur)

Cytosine arabinoside is currently used as chemotherapy for leukemia and cancer. For treating PML, it's commonly given through a shunt (intrathecally) into the brain and/or directly into a vein (intravenously). Experienced neurologists may administer ara-C through the shunt at doses of 10mg/m<sup>2</sup> for three days, followed by 10mg/m<sup>2</sup> twice a week for two weeks, then 20-30mg/m<sup>2</sup> weekly thereafter. The common dose of ara-C given into a vein is 2mg/kg in five-day cycles, either every 15 days or monthly.

Side effects of ara-C include nausea, constant fevers and bone marrow toxicity. These effects depend upon the dose and schedule and vary in severity. Ara-C can harm unborn children in pregnant women.

Monitoring of blood work is necessary, including daily platelet, leukocyte counts and bone marrow exams throughout treatment. Some doctors give a dose of G-CSF (granulocyte colony stimulating factor, Neupogen) for one week before ara-C treatment to relieve bone marrow toxicity. Prednisone may help towards diminishing side effects.

While ara-C is considered standard-of-care for people with PML, many forego treatment due to its invasiveness, side effects and low

success rate. While earlier studies showed mixed results, a recent study suggests that ara-C has little-to-no benefit for treating PML. For more information, read page 3.

## Highly Active Anti-HIV Therapy (HAART)

Before the time of potent anti-HIV therapy, there was little encouraging news about PML. But some people using potent anti-HIV therapy now report symptom-free survival after a PML diagnosis of over five years and counting. Factors associated with improved survival include using an anti-HIV regimen with protease inhibitors and changing to new regimen following PML diagnosis.

While there are no standard of care guidelines for anti-HIV therapy and PML, it would be fair to make a few assumptions based on accumulating information. After a presumptive or definitive PML diagnosis, starting or changing a HAART regimen including a protease inhibitor seems advisable.

Experienced neurologists who choose to treat PML with anti-HIV drugs will typically chose a regimen that includes AZT (zidovudine, Retrovir), as it has been shown to cross the blood-brain barrier and is effective, at high doses, in treating other HIV-related brain disorders like dementia.

The dose of AZT used in this case is 1,000-1,200mg daily (lower doses are not as effective at crossing the blood-brain barrier). This is higher than the current recommended daily dose for AZT, which is 500-600mg, daily. Doses may be adjusted according to one's ability to tolerate the treatment.

Other anti-HIV treatments may be substituted if a person cannot tolerate AZT. Other drugs that cross the blood-brain barrier include: d4T (stavudine, Zerit), ddI (didanosine, Videx), ddC (zalcitabine, Hivid), 3TC (lamivudine, Epivir), amprenavir (Agenerase) and nevirapine (Viramune). For more information, call Project Inform's Hotline and ask for *Anti-HIV Therapy Strategies*.

## Experimental Treatments

A group in France has looked at using cidofovir (Vistide) for PML. People received cidofovir through an expanded access program while also using HAART. While this observational study is quite small, an early look at survival rates suggests that cidofovir may be useful for some people. A second, larger Italian study also suggests it may be useful in treating PML.

The dose of cidofovir used in the Italian study was 5mg/kg every week for the first two weeks then 5mg/kg every other week. Cidofovir is a very difficult drug to take with many side effects. It is given by injection directly into the vein (intravenously) and has to be given with probenecid to lower the risk of developing kidney toxicities. However, even with the use of probenecid, a fair number of people

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have problems tolerating the drug. Cidofovir is an approved treatment for CMV retinitis. For more information, see page 4.

Two other experimental drugs that might have some value in treating PML include topotecan and alpha interferon. Many recent publications about PML note that topotecan is under study for PML, but in fact the one small study that had been developed was closed because it couldn't attract volunteers. Currently no study is evaluating alpha interferon treatment for PML, though the drug is available *off label*, as it is approved for treating hepatitis as well as Kaposi's Sarcoma (KS). No experimental dosing information is available on alpha interferon for treating PML.

## Commentary

Currently, many doctors assert that PML is not treatable. However, some individuals have responded to various treatments. Obviously, the wise use of anti-HIV therapy, for unknown reasons, appears to dramatically impact survival after a PML diagnosis. Because anti-HIV therapy does not inhibit the JC virus itself, the benefits from potent anti-HIV therapy on PML can only be assumed to be caused by improvements in the immune system realized when HIV replication is arrested.

People with PML have had varying degrees of success with the approaches reviewed here. It's important to recognize, though, that successful treatment at best usually involves only stabilization or partial resolution of symptoms, even when brain lesions shrink. This is different from being fully symptom-free.

Despite an arrest or decrease of lesions in the brain, someone with PML may experience permanent symptoms that may include weakness on one side of the body or limbs, loss of vision and/or impairment of certain functions (e.g. slurred speech, memory loss, disorientation, loss of balance, etc), even if survival is extended and PML lesions stabilize or improve. In one case of complete resolution of brain lesions after starting HAART, despite disappearance of lesions, partial vision loss caused by the damage of the JC virus in the part of the brain that controls sight remained permanent.

This suggests that it's wise to treat PML early and aggressively as the damage that's allowed to continue unchecked may become permanent. It is not uncommon, however, after an injury or disease for the brain to repair somewhat, or for other parts of the brain to compensate and for symptoms associated with the condition to improve.

PML is difficult to study. Factors that make it difficult include the rapid onset of symptoms, similarities to other complications (such as toxoplasmosis), and the fact that some people spontaneously recover or stabilize for unknown reasons. Most information about PML treatments now comes from small studies and

anecdotal reports. Some very preliminary studies suggest that looking at JC virus levels in blood, after starting treatment for PML, may provide useful information in checking how PML is responding to treatment.

PML diagnosis procedures remain 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 far more acceptable to many people.

Among people with HIV, about 70% with and 30% without PML have detectable JC virus in the blood. Given the large percentage of people with measurable levels of JC virus without PML, using a blood test as a way to diagnose PML is not practical. Far too many people without PML could be misdiagnosed as having PML. Exploring the use of cerebral spinal fluid (CSF) to diagnose PML may provide a middle ground. For more information, see page 4.

## Supplemental Information

**ARA-C.** In the time before protease inhibitors, Dr. Britten of Columbia University presented results from a small study involving 26 people with PML diagnosed by brain biopsy. Dr. Britten treated 13 of them with ara-C and the maximum tolerated dose of either AZT or ddI. Ten of the 13 had CD4+ cell counts under 50; the mean CD4+ cell count of this group was 106, ranging from 7 to 690. Eight people had their symptoms stabilize or improve: four of them for seven months to two years, and the other four for six weeks to six months. Volunteers who did not respond to ara-C treatment had large lesions, major deficits or brain stem disease. She suggested that people with a CD4+ cell count over 200 may have a better chance for stabilizing symptoms, spontaneously or with anti-HIV treatment. Numerous other studies indicate that there may be no difference in survival time with ara-C use, but partial resolution of symptoms may occur with multiple cycles.

**ANTI-HIV THERAPY.** An Atlanta group has reported on factors associated with survival among 375 people with HIV and PML. The median survival after a PML diagnosis was one month, overall (including people with PML in the pre-protease inhibitor era). Additionally, about 85% of those diagnosed with PML had died within six months of diagnosis. Longer survival (more than six months) was associated with using protease inhibitors and other anti-HIV therapies.

In a study reported by a French group, 71 people diagnosed with PML between January 1990 and September 1997 were observed for factors influencing survival. Many were diagnosed before the protease inhibitor era. PML was the first AIDS defining event for about half the participants. It was the event that led to an HIV



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diagnosis in eight of the volunteers, suggesting it was the first serious symptomatic illness they experienced. A little less than half of the individuals had been on anti-HIV therapy before PML diagnosis. This study showed that among people who had previously been on anti-HIV therapy, those who modified their regimen after the PML diagnosis had a longer survival (ten months) compared to those who did not change therapies (three months). Moreover, those individuals employing an anti-HIV regimen that included a potent protease inhibitor had longer survival (twelve months compared to 3.5 months among those not using protease inhibitors). Among people using a protease inhibitor-containing regimen since their broadened availability in 1996, over half (54.2%) are still alive. Seven people have survived more than two years after their PML diagnosis. *(Note: This is a summary of data presented in 1998. Other groups more recently report survival rates of five years and counting, after PML diagnosis, with the use of anti-HIV medication including a protease inhibitor.)*

In Spain, another group studied the use of HAART in 13 people with PML (12 also used ara-C). The median survival time after PML diagnosis was 273 days. Historical results suggest that in this particular population, survival is typically about 72 days. Three-drug therapy nearly quadrupled survival time post PML diagnosis.

**NEW TECHNIQUES.** Dr. Major, of the National Institutes of Health, has presented data showing that 80% of people with PML confirmed by brain biopsy have JC virus in the cerebral spinal fluid (CSF). While this is a step toward a simpler diagnostic tool, it's still not without problems. Dr. Major presented information showing a small number of people with other (not PML) brain-related conditions also had measurable JC virus in the CSF. When it comes to brain-related AIDS conditions, proper diagnosis is critical. For

example, herpes infections in the brain can produce symptoms similar to those of PML, yet these infections may be readily and easily treated with a 21-day course of acyclovir (Zovirax) given directly into a vein (intravenously). Until the technology is further refined, using CSF as a primary mode of diagnosis may lead to misdiagnosis. The beginning of research into this field is long overdue, however, and these first steps toward less invasive diagnostic procedures are extremely important.

### The Bottom Line

- PML is a rare condition affecting the brain, caused by a virus, called the JC virus.
- PML is difficult to diagnose; definitive diagnosis requires a brain biopsy.
- The only treatment is ara-C, a toxic drug delivered through a shunt directly into the brain.
- Many people choose to not use ara-C due to uncertainty about its benefits.
- Potent anti-HIV therapy, including a protease inhibitor, has had a profound positive effect on PML.
- Using protease inhibitors after a PML diagnosis, as well as changing to a new anti-HIV regimen with a protease inhibitor, has resulted in quadrupling of survival rates. Some people are surviving five years and counting after an PML diagnosis.
- The CMV drug, cidofovir, has in shown some evidence of benefit in treating PML.

### Cidofovir

Results from an Italian study suggest that cidofovir (Vistide) may be useful for people with progressive multifocal leukoencephalopathy (PML). This recent study involved 40 people with PML all of whom were taking potent anti-HIV therapy. Fourteen were also given cidofovir, a drug approved for the treatment of cytomegalovirus (CMV). The dose of cidofovir used in this study was 5mg/kg every week for the first two weeks then 5mg/kg every other week. People receiving cidofovir had a more pronounced increase in CD4+ cell counts and prolonged survival compared to people receiving only potent anti-HIV therapy.

Further analysis of the results show that several factors contributed to prolonged survival: use of cidofovir, lower JC virus levels at the start of the study and starting potent anti-HIV therapy prior to developing PML.

Cidofovir is a very difficult drug to take. It has to be given by injection directly into the vein (intravenously) and has to be given with probenecid to reduce the risk of developing kidney toxicities. Even with the use of probenecid, a fair number of people have problems tolerating the drug. Still, the side effects of cidofovir seem less significant than those of ARA-C and pale when compared to the effects of a bad case of PML. While there are no standard of care guidelines for PML, this study suggests that the addition of cidofovir to potent anti-HIV therapy should be considered. However, the side effect profile for cidofovir is still of great concern.