

Case Discussions

National HIV Curriculum Podcast

# PML: Evaluation and Management

June 24, 2025

Season 2, Episode 7

National HIV Curriculum Podcast Editors Dr. Jehan Budak and Dr. Aley Kalapila discuss their approach to diagnosing and managing Progressive Multifocal Leukoencephalopathy (PML) in a person with advanced HIV.

Topics:

- OIs and HIV
- PML
- JC virus
- PML-IRIS

## **Jehan Z. Budak, MD**

Associate Professor of Medicine  
Division of Allergy & Infectious Diseases  
University of Washington

### [Disclosures](#)

**Disclosures for Jehan Z. Budak, MD**

None

**Aley G. Kalapila, MD, PhD**

Professor of Medicine

Division of Infectious Diseases

Emory University School of Medicine

Grady Health System

[Disclosures](#)

**Disclosures for Aley G. Kalapila, MD, PhD**

None

## Transcript

Read along with the audio or jump to a particular chapter.

In this episode:

- [Introduction](#)
- [Differential Diagnosis](#)
- [Diagnostics](#)
- [PML Overview](#)
- [PML Diagnosis](#)
- [PML Management](#)
- [Trialing Corticosteroids](#)
- [PML Clinical Trajectory](#)
- [Summary](#)
- [Credits](#)

## [introduction](#)[00:00] Introduction

Hello everyone. I'm Dr. Jehan Budak from the University of Washington in Seattle, and welcome to the National HIV Curriculum Podcast. This podcast is intended for health care professionals who are interested in learning more about the diagnosis, management, and prevention of HIV.

I'm back with my colleague, Aley Kalapila, an ID [infectious diseases] physician at Emory University in Atlanta. Hi, Aley.

Dr. Kalapila

Hi, Jehan. Hi everyone. Excited to be back here and looking forward to this discussion.

Dr. Budak

So today we're going to discuss PML (or progressive multifocal leukoencephalopathy), which is an infection of the CNS (or central nervous system) in immunocompromised individuals, especially in those with advanced HIV, caused by the JC virus (or the John Cunningham polyomavirus).

So, now that we've set that stage, let's start with the case of your patient, Aley, who you had first met while he was admitted to the hospital. He is a 58-year-old man who's had HIV for 20 years. And at the time of his diagnosis, recalls being started on ART [antiretroviral therapy] and trimethoprim-sulfamethoxazole. He's taken his meds intermittently for the last 18 years, but has been completely off of them for the past two years due to pill fatigue. He has been doing well and was fully employed at a restaurant until four months before you met him. But since that time, he's had progressive cognitive decline to the point that he now lives with his sister.

And in the week prior to admission, he had increasing forgetfulness and behavior that his sister described as odd, such as opening the front door to urinate outside. On the day he was admitted, his sister found him down in the bathroom. She said that he appeared drowsy and weak and she thought that he had had a stroke, so she called 911. And, when the ambulance arrived, he had a witnessed generalized tonic-clonic seizure, for which he received lorazepam and the seizure ended. And though he had no focal neurologic deficits on exam in the emergency room (or ER) he was admitted for an expedited workup of seizure in a person with advanced HIV. And at the time of admission, his CD4 cell count was 52. So, thoughts?

## [differential-diagnosis](#)[02:01] Differential Diagnosis

Dr. Kalapila

Well, he has an indolent presentation, and he's experiencing basically chronic cognitive decline. Now, there are a lot of noninfectious etiologies to explain chronic cognitive decline that can affect all people regardless of their HIV status, so things that we think about would be dementia or cancer metastasized to the brain, for example. But we are doing a podcast for the National HIV Curriculum (NHC) after all, and so I want to obviously focus on infectious etiologies given the infectious etiologies of chronic cognitive decline as well as seizure activity in a patient with advanced HIV. Now, I'm comfortable moving typical pathogens that cause a more fulminant presentation further down on my differential diagnosis.

So, in prior episodes, we have discussed the potential diagnoses for persons with advanced HIV who present with headaches, seizures, or focal neurologic deficits, so I'm not going to rehash all of those. But, this patient had a chronic course, like we just said, and that doesn't really seem to me very consistent with bacterial meningitis such as pneumococcal meningitis or meningococemia, for example. Now, on the other hand, syphilis certainly could present this way. It can have an indolent presentation and with new neurologic

symptoms and a CD4 count less than 100, I would also think about, for instance, cryptococcal meningitis in the differential. But, I will say that usually a presentation of cryptococcal meningitis does tend to be more acute or subacute, which I think is a little bit less likely in this scenario.

Now, with his seizure, you want to think about protozoal causes such as toxoplasmosis, which we have also discussed in prior NHC Podcast episodes. And, you know, his presentation is not very consistent with a viral encephalitis like one due to herpes simplex virus for instance. But given the constellation of findings, chronic cognitive decline, the CD4 count less than 50, the seizure activity, the diagnosis that is probably highest on my differential in the virus bucket is JC virus causing PML. I would also consider CNS lymphoma given his cognitive decline and seizures as well.

### [diagnostics](#)[04:10] **Diagnostics**

Dr. Budak

Okay, so, based on that sort of differential diagnosis, what sort of tests would you like to order?

Dr. Kalapila

Aside from routine labs like a CBC [complete blood count] and a CMP [comprehensive metabolic panel], given the neurologic symptoms and the low CD4 count, I would still proceed with a broad infectious workup. Because, as you and I both know, these patients can have multiple processes that happen at the same time, right? So, you don't want to necessarily anchor and then miss something. So, as a good starting point, given the behavioral changes in the seizure, I think the first step is to get a non-contrast head CT to look for any acute intracranial anatomic pathology.

Dr. Budak

And the report said quote, "No acute intracranial process."

Dr. Kalapila

Well, so then from a lab perspective, I would want to get a serum cryptococcal antigen, or a serum CrAg as we often refer to it. Again, given the low CD4 count and neurologic symptoms, I would also check a serum toxoplasma IgG. We should definitely do syphilis serologic testing since it is on the differential. And then from a more advanced imaging standpoint, I'd like to get an MRI brain to look for any structural abnormalities that we may not necessarily have seen in a non-contrast head CT, as well as order a spot EEG (or an electroencephalogram), given the seizures. I will also add that because of, again, advanced HIV, neurologic symptoms, a thorough workup here would also include a lumbar puncture (or an LP).

Dr. Budak

Okay. And then before we talk about the MRI and the EEG, what would you send from the CSF (or cerebrospinal fluid)?

Dr. Kalapila

Okay, so before I go into specifics, again, like we said, we are going to keep a broad differential here because of his low CD4 count. And so, it is reasonable to send CSF studies for all potential pathogens to rule out etiology such as cryptococcus, neurosyphilis, tuberculosis, for instance, if he has risk factors for that, and encephalitis due to herpes viruses. Since CNS lymphoma is possibly on the differential as well, you should consider adding a PCR [polymerase chain reaction] for Epstein-Barr virus (or EBV). And then finally, honing in on PML specifically, we should send off CSF PCR testing for JC virus.

Dr. Budak

So, in this patient, the serum CrAg and serum toxoplasma IgG were negative, and the serum RPR [rapid plasma reagin] was non-reactive as well.

Dr. Kalapila

Great. So, with those negative results, I think that CNS toxoplasmosis and neurosyphilis are much less likely. But then can you tell me a little bit more about some of the other results?

Dr. Budak

Certainly. So as for his CSF studies, he had a broad infectious workup as you requested, that was largely negative except for a positive CSF JC virus PCR. His EEG showed seizures and his MRI brain showed patchy asymmetric T2 hyperintensities in the subcortical white matter of the right frontal, parietal, and occipital lobes.

Dr. Kalapila

That MRI showed no ring-enhancing lesions, which in my mind rules out toxoplasma, as well as CNS lymphoma. Now, given the white matter changes on the MRI, as well as the positive JC virus from the CSF, *and* we have a congruent history that is also consistent with a diagnosis of PML.

### [pml-overview](#)[07:21] **PML Overview**

Dr. Budak

So, for some background about PML, it is a focal demyelinating disease of the CNS caused by reactivation of JC virus in the setting of advanced immunosuppression and is most commonly seen in people with advanced HIV. And anywhere from 20 to 70% of individuals worldwide have already been exposed to JC virus. And when PML happens, it's actually due to reactivation of that virus in the setting of immunocompromise.

The clinical presentation can really vary and depends on the location of the brain that is affected. And in general, symptoms can include cognitive and behavioral changes, sensory and motor deficits, ataxias, aphasias, visual changes, and even seizures, as occurred in this case. Aley, what else do you have to add to that?

Dr. Kalapila

So, as you said, it typically presents with focal neurologic deficits that correlate with the site of the lesions. Typically, it is an insidious onset with a steady progression of these deficits that can worsen over time. Now, the presenting symptoms can often be mistaken for a stroke really, and pretty much any part of the central nervous system (or CNS) can be affected, although usually the spinal cord and optic nerves are rarely involved. Other uncommon symptoms that you may see in patients with PML include things like fever, headache, or acute encephalopathy.

### [pml-diagnosis](#)[08:40] **PML Diagnosis**

Dr. Budak

Now, moving on to diagnostics. As you had implied, the diagnosis of PML is typically presumptive based on clinical symptoms and neuroimaging findings. Although a CT scan may show white matter hypodensities, it is much less sensitive than an MRI, which is the recommended neuroimaging to diagnose PML. The MRI should demonstrate white matter changes or lesions present in the area of the brain that corresponds to the neuro

deficits noted on history or exam. And a classic description of PML is that of a T2 hyperintense lesion in the deep white matter, which is what this patient had.

These lesions tend not to respect the border between the white matter and adjacent cortical gray matter, and the multiple lesions can be seen—a solitary lesion tends to be predominant. And in contrast to CNS toxo and primary CNS lymphoma, with PML, it would be rare to see mass effect or displacement of normal structures. So, now that we've talked about imaging, Aley, can you tell us if CSF analysis is something you routinely use to diagnose PML?

Dr. Kalapila

So, confirmation of the diagnosis would be ideal, and that can be done by detecting JC virus DNA from the CSF using PCR testing. But, the sensitivity of the PCR test can be variable and based on the assay, as well as the assay's lower limit of detection. So, what that means is that it can be falsely negative if there is a very low JC viral load.

Now, if your first JC virus PCR test off the CSF is negative, it is reasonable to repeat your CSF PCR studies, especially if you've been unable to confirm an alternate diagnosis that would explain the patient's symptoms. And that repeat CSF test could be positive. But all this to say, an undetectable JC virus DNA in the CSF does not preclude the diagnosis of PML, especially if you have a patient with a clinical presentation and neuroimaging that is congruent with PML, and you have done your due diligence and ruled out other etiologies to explain their symptoms.

The gold standard though, for diagnosing PML is actually a brain biopsy. But as you can imagine, that's not something that we do very frequently.

#### [pml-management](#)**[10:51] PML Management**

Dr. Budak

Okay. Now that we've talked about diagnosis, let's switch gears and talk a bit about management, which is straightforward. It is just giving ART for immune reconstitution, and that is because currently there is no antiviral or immunomodulatory therapy recommended specifically for the treatment of PML.

Dr. Kalapila

Yes, that is true. The key aspect of management for PML is really to restore JC virus-specific immunity, which antiretroviral therapy can do. And so, because of that, you absolutely want to initiate ART sooner rather than later and not delay ART initiation.

Now, if a person is already on antiretroviral therapy and has an undetectable HIV RNA or an undetectable HIV viral load, at the time of their PML diagnosis, there is no role to intensify ART regardless of their PML status. And from a symptom perspective, having a good conversation with the patient and their support system is really, really important here because there's no way to determine or predict how a patient's PML will or will not progress with antiretroviral therapy.

Dr. Budak

Aley, can you expand on that a little bit?

Dr. Kalapila

Sure. So, you know, when I have a patient with PML, I usually tell them that in general, PML can get better, stay the same, or worsen. Now, factors associated with a worse prognosis include a high plasma HIV RNA at

the time of their diagnosis, a poor virologic response to antiretroviral therapy, and PML lesions in the brainstem.

Now, the presence of any of these factors may impact how I counsel the patient. If a patient were to clinically deteriorate, it is sometimes very difficult to determine whether or not this is due to a progression of underlying PML, or if their clinical deterioration is due to PML immune reconstitution inflammatory syndrome (or PML-IRIS), which we can see in about 20% of cases.

Now, if a patient were to clinically worsen despite HIV RNA suppression, then you can consider repeat neuroimaging because this may be helpful in looking for any interval change compared to their prior imaging. If the repeat imaging shows worsening inflammation or worsening perilesional vasogenic edema, then that would suggest that the clinical deterioration that you're seeing is attributable to PML-IRIS.

But, you know, these cases are really very challenging to diagnose. And, I often will have a very detailed conversation, extensive conversation with the neuroradiologist reviewing the films to help me determine what exactly is the cause of the patient's clinical deterioration. But, the bottom line here is that if there is concern for PML-IRIS, then it's very reasonable to do a trial of corticosteroids as part of the management for PML-IRIS.

### [trialing-corticosteroids](#)**[13:44] Trialing Corticosteroids**

Dr. Budak

And if you are trialing corticosteroids for someone in whom you suspect PML-IRIS, what is the duration of therapy? And what do you expect to see?

Dr. Kalapila

So, first and foremost, you have to continue antiretroviral therapy. That's a given. For people who were started on corticosteroids, there's really no consensus on optimal dosing or duration. But, many experts would consider giving corticosteroids for about 4 to 6 weeks, monitoring clinical symptoms, and then repeating the neuroimaging after 4 to 6 weeks because that repeat imaging can be helpful in guiding the duration of the steroids. Again, as I've said before, it is extremely important when all of this is happening to have a discussion with patients and their support networks about goals of care.

Dr. Budak

So, what happened to your patient?

Dr. Kalapila

So unfortunately, despite the fact that he had HIV RNA suppression (or HIV viral load suppression) antiretroviral therapy, he continued to have intermittent seizure activity requiring intensive anti-epileptic medications. And unfortunately, he ended up falling out of care.

Dr. Budak

That's disappointing to hear.

### [pml-clinical-trajectory](#)**[14:53] PML Clinical Trajectory**

Dr. Budak

Speaking of clinical trajectory, in my experience with just a few patients with PML, most individuals have passed away. That being said, I do have one clinic patient who was diagnosed with PML 15 years ago, went on

hospice, and then came off, and is still coming to clinic and is relatively fine.

Dr. Kalapila

Yes, you know, most of the time the prognosis is poor and the one-year survival is approximately 60%. But as we've mentioned before, it is hard to predict outcomes, and there can be a subset of patients who do have improvement, although their neurologic deficits usually do persist.

So, for example, I do have some patients who are still alive and clinically stable with persistent neurologic deficits, one who has profound dysarthria, and another one who still has unilateral lower extremity weakness and needs an assistive device. But both of them have been doing very well on their antiretroviral therapy without any further progression of their deficits for at least the last decade.

Dr. Budak

And I think one last thing to acknowledge is that this is a really uncomfortable situation to have to tell patients that we have no idea what's going to happen, and that there is nothing to do except for to continue ART. So, on that somber note, let's wrap up.

### [summary](#)**[16:06] Summary**

Dr. Budak

In summary, PML is a demyelinating disease of the brain caused by JC virus in persons with advanced HIV and low CD4 counts. The diagnosis is presumptive based on the clinical symptoms and neuroimaging findings, and MRI is much more sensitive than CT for diagnosing PML.

Confirmation of the diagnosis is made by detecting JC virus DNA in the CSF. Management consists of effective ART, and the prognosis is guarded and neurologic deficits may be permanent. So, with that, Aley, thank you for a rich, albeit somber discussion. And I'll see you next time.

Dr. Kalapila

Thanks, Jehan. See you next time.

### [credits](#)**[16:45] Credits**

Transcripts and references for this podcast can be found on our website, the National HIV Curriculum at [www.hiv.uw.edu](http://www.hiv.uw.edu). The production of this National HIV Curriculum Podcast was supported by Grant U10 HA32104 from the Health Resources and Services Administration of the U.S. Department of Health and Human Services. Its contents are solely the responsibility of the University of Washington IDEA Program and do not necessarily represent the official views of HRSA or HHS.