Case Discussions

National HIV Curriculum Podcast

Diagnosis, Evaluation, and Management of Chronic Diarrhea in People with HIV

June 23, 2026

Season 3, Episode 4

National HIV Curriculum Podcast Editors Dr. Jehan Budak and Dr. Aley Kalapila present a clinical case study to discuss the evaluation and management of chronic diarrhea in people with HIV, including cryptosporidiosis, cystoisosporiasis, and microsporidiosis.

Topics:

- Diarrhea
- cryptosporidiosis
- cystoisosporiasis
- microsporidiosis
- multiplex enteric PCR
- opportunistic infection

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Disclosures
Disclosures for Jehan Z. Budak, MD
None

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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 & Background
- Differential Diagnosis and Workup

- Bacterial Pathogens
- Viral Pathogens
- Parasitic Pathogens
- Clinical Manifestations
- Diagnosis & Treatment
- Diagnostics for Other OI Pathogens
- Preferred Treatment Options
- In Closing
- Credits

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introduction-amp-background**[00:00] Introduction & Background**

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, looking forward to this episode.

Dr. Budak

So, today we are going to talk about diarrhea as initial presentation in a person who was newly diagnosed with HIV, and we'll get right into the case, which is that of a 34-year-old man, who was evaluated in the emergency room (or ER), with profuse diarrhea for several months. At the time he presented to the ER, he was unaware of his HIV status. He describes significant nausea and 5 to 7 large watery bowel movements each day, and with this, he has noticed a 15 pound weight loss. He denies any recent travel or unusual food ingestions. He lives with several other family members, none of whom who have been ill, and he denies any drug or alcohol use but endorses having multiple condomless sexual encounters with men and women over the last several years. In the ER, his vital signs were notable for a heart rate of 105, so slightly tachycardic, with systolic blood pressures in the low 100s, and notably he was afebrile.

On exam, he had dry mucus membranes, a thin cachectic appearance, and mild abdominal tenderness. And we find out that labs were notable for a positive HIV antigen-antibody test. The HIV-1/2 antibody differentiation assay, and an HIV-1 RNA (or viral load) both pending. He has mild leukopenia and anemia on complete blood count, and his chemistry panel was notable for mild hypokalemia. So, with all that, Aley, what is your approach to working up this person's diarrhea?

differential-diagnosis-workup**[01:55] Differential Diagnosis and Workup**

Dr. Kalapila

Okay. So, based on his presentation, what I'm most concerned about is that he has a CD4 count that might be very low, and this of course really broadens our differential. Now, in people living with HIV, diarrhea can be caused by the standard enteric pathogens that we can think of, like salmonella or shigella, regardless of their CD4 count, but when the CD4 count is very low, we have to think more seriously about opportunistic infections or opportunistic pathogens. The other thing to take into consideration when looking at this case is

to also look at the chronicity of his symptoms because that really helps you to refine your differential diagnosis. Now, in this specific case that you've told me about, the prolonged course makes me think that this is more of an OI [opportunistic infection] rather than a standard self-limiting diarrheal illness. So, just as we've done in other episodes, I'll take a look at this differential diagnosis using the bacterial, viral, fungal, and parasitic categories or buckets.

bacterial-pathogensnbsp**[02:55] Bacterial Pathogens**

So, first, looking at bacterial pathogens, I think of common enteric pathogens, which often present with fever, abdominal pain or blood in stool. And so, these could include things like *E. coli,* shigella, campylobacter, salmonella... And we also need to keep *C. diff* in the differential, which while it's classically associated obviously for *C. diff* with recent antibiotic use or hospitalizations, you can also get community acquired infections as well.

Dr. Budak

And just to emphasize, these organisms that you just mentioned can affect anyone regardless of CD4 count, and we don't even have this patient's CD4 cell count back yet.

Dr. Kalapila

Yes, absolutely, that's a great point. The only thing I would add here is that people who have lower CD4 counts tend to have more severe presentations with their diarrheal illness, such as salmonella, which can actually cause invasive disease in people with HIV.

Dr. Budak

And some of the organisms you mentioned like *E. coli*, shigella, et cetera, can be transmitted sexually. Are there any other bacteria that you'd like to include in this category?

Dr. Kalapila

So, I would also think about organisms like MAC (or *Mycobacterium avium* complex) in people living with HIV, particularly advanced HIV, especially when CD4 counts are less than 50. Disseminated MAC can present with diarrhea often as their predominant symptom. In those cases, I would also ask about systemic or constitutional symptoms such as fever or night sweats, weight loss, fatigue, all of these things can present when someone has disseminated MAC. And then, on labs, you might see an anemia or an elevated alkaline phosphatase, which can also provide additional clues that the person might have disseminated MAC.

viral-pathogensnbsp**[04:32] Viral Pathogens**

Dr. Kalapila

Now, moving to the viral bucket, now there are several viruses that can cause diarrhea as well, right? So, respiratory viruses, such as influenza and adenovirus, can be associated with GI [gastrointestinal] symptoms, but these presentations are usually acute, self-limited, and they don't tend to be as severe as a diarrhea that this patient was experiencing that you've just described.

Norovirus is another consideration, and this can cause both a profuse voluminous diarrhea often accompanied with vomiting. And then less common than the others I mentioned, we also have to think about CMV (or cytomegalovirus). CMV colitis often presents with abdominal pain and diarrhea in people with advanced HIV, especially when CD4 counts are less than 100, but these are often associated with blood in your stool. I think those are the main viral pathogens that I would consider for the differential diagnosis in this specific clinical scenario.

parasitic-pathogens**[05:27] Parasitic Pathogens**

Dr. Budak

And then what about the parasites?

Dr. Kalapila

So, for parasites, usually I think about giardia, which can occur with any CD4 count, causing an acute watery diarrhea, but can also present more intermittently with foul smelling stools, significant flatulence and bloating. I also think about *Cryptosporidium*, as well *Cystoisospora*, and *Microsporidia*. Although technically, I guess *Microsporidia* is now classified as a fungus. And then all of these are considered, except for giardia, the other three are considered as opportunistic pathogens that typically affect patients with low CD4 counts, usually under 100. And they are classically associated with a chronic profuse watery diarrhea, and out of *Cryptosporidium*, *Cystoisospora,* and *Microsporidia*, the one that we see most frequently in clinical practice, or at least I have seen most frequently in clinical practice is *Cryptosporidium*.

Dr. Budak

Now, let's talk a little bit about diagnosis. So, when I'm working up diarrhea, the first test I send is a multiplex stool PCR [polymerase chain reaction], and it covers— enteric panel here— covers approximately 22 different targets, and for the organisms that we've discussed, or rather that Aley has mentioned, it would detect *E. coli*, shigella, campylobacter, salmonella, *C. difficile*, norovirus, giardia, and *Cryptosporidium*. And for the more specialized tests, whether it be stains, specific PCRs, or a stool ova and parasite exam, I personally don't send right away, and then I wait to see what the stool PCR shows before expanding the workup.

Dr. Kalapila

So, my approach is a little bit different. If *Microsporidia* or *Cystoisospora* are on my differential, I will send those tests at the same time as the initial stool PCR, because they actually send out labs at my institution, and it takes a long time to get those results back, I would like to avoid delaying my diagnosis. So, in this case, I would go ahead and send them upfront because I am concerned based on the presentation that you've described: his CD4 count being less than 100, and of course, the chronic nature of these symptoms. All of these make me think that *Microsporidia* and *Cystoisospora* are on the differential along with *Cryptosporidium* as well.

Dr. Budak

That's a great point, Aley. Thank you. And then also just to add, if disseminated MAC is on your differential, you'd also want to send AFB [acid-fast bacillus] blood cultures.

clinical-manifestations**[07:43] Clinical Manifestations**

Let me move ahead and talk about what we have found in his case. His HIV-1/2 antibody differentiation was positive, his CD4 cell count was 32, consistent with what Aley was suspecting, and his viral load was 76,000 copies/mL. Later that day, his stool PCR came back positive for *Cryptosporidium*. So, Aley, I think I know the answer to this, but were you or are you surprised by that result?

Dr. Kalapila

No, not at all surprised. So, given how low his CD4 count is, *Cryptosporidium*, *Cystoisospora,* and *Microsporidia*, all high on my differential, and as we've alluded to, all three of these organisms can cause an acute to subacute, non-bloody, high-volume watery diarrhea, which is exactly what happened in this patient's case. Typically, for these types of infections, they occurred through ingestion, and the most severe

presentations usually occur when the T-cell count is less than 200. We can also see severe dehydration, malabsorption, anorexia, and low-grade fevers, and of course, electrolyte derangements because of the dehydration. It is unusual to see extraintestinal disease, but it can happen. So, for example, some *Microsporidia* species can cause encephalitis or ocular involvement, and *Cystoisospora* can rarely cause biliary disease, including in AIDS cholangiopathy as well.

diagnosis-amp-treatment**[09:02] Diagnosis & Treatment *Cryptosporidium***

Dr. Budak

So, Aley, you've been talking about the three parasitic OIs, and I'm going to first focus this in on *Cryptosporidium*, which is what this patient had. So, we diagnosed this person's *Cryptosporidium* with a stool PCR. If PCR was not available, let's say, diagnosis would then rely on stool microscopy using acid-fast staining, or direct immunofluorescence to identify oocysts in the stool, though these methods tend to be less sensitive. Stool antigen immunoassays are another option, but their sensitivity can be very variable. And it's important to note that routine ova and parasite (O&P) testing does not detect *Cryptosporidium*, *Cystoisospora*, or *Microsporidia*. So, Aley, when you were talking about ordering these tests in addition to the enteric PCR, what were you sending, and do you usually send one stool sample or do you send multiple, especially with regards to O&Ps?

Dr. Kalapila

In my experience, one sample is usually sufficient, especially for the diagnosis of cryptosporidiosis, and especially when PCR is available. Now, if PCR isn't accessible or a suspicion remains high despite a negative test, then you can definitely do repeat sampling, that can be helpful, especially when patients have much milder cases of *Cryptosporidium*.

Dr. Budak

That makes sense. And then, so in this person's case with the *Cryptosporidium*, how do you approach treatment of that?

Dr. Kalapila

The cornerstone for treatment for cryptosporidiosis is really antiretroviral therapy (or ART). That is absolutely key, not just for *Cryptosporidium*, but also for *Cystoisospora* and *Microsporidia* as well. So, it really is immune reconstitution that is what leads to clinical improvement and eventually resolution as well of these infections. Now, unfortunately, our antimicrobial options for *Cryptosporidium* are pretty limited, especially in the absence of antiretroviral therapy. So, the antimicrobials that we would use are nitazoxanide or paromomycin, but they often can be expensive, they are difficult to obtain sometimes, often can be affected by drug shortages that may exist. And even when they're available, personally, their efficacy is modest in the absence of immune reconstitution.

So, when we do use them, I would say that we use them as an adjunct to antiretroviral therapy, so we would do ART as well as using one of these antimicrobials, and typically the duration is often 14 days, which is what we typically do for patients with this type of an infection.

Dr. Budak

I agree with the comments you're making about the nitazoxanide and the paromomycin and with regards to the difficulty in obtaining them, because I've had those experiences here as well. And in your experience, you were mentioning that waiting for immune recovery treatment duration is usually about 14 days, but in your experience, how quickly do patients typically improve when they have *Cryptosporidium*?

Dr. Kalapila

Since improvement really depends on immune recovery, it can take weeks to months, especially for patients like this, who are very severely immunosuppressed with T-cell counts less than 100. So, in the meantime, you would do supportive care for these individuals with hydration, electrolyte repletion, antiemetics, if they're nauseous, *Cryptosporidium* can cause a lot of nausea too. And then of course for symptom control, once we've ruled out invasive bacterial toxin-mediated causes, we can often use things like loperamides, antimotility agents, and in severe cases, I found actually even tincture of opium to be more effective as well.

And so, these agents can help stabilize the patient, give them some symptomatic relief while we wait for the ART to do its heavy lifting to restore their immune function. And, because there are no highly effective antimicrobial therapies for *Cryptosporidium*, chronic maintenance therapy isn't recommended. So, you would do those 14 days of therapy and then you would really stop and focus primarily on immune recovery with antiretroviral therapy.

diagnostics-other-oi-pathogens**[12:48] Diagnostics for Other OI Pathogens**

Dr. Budak

So, now let's shift away from *Cryptosporidium* and towards the other organisms that can present similarly, cystoisosporiasis and microsporidiosis. And I'll highlight some similarities and differences between those two, between cystoisosporiasis and microsporidiosis. So, as we've discussed, as you've mentioned, Aley, the clinical presentation across all three, *Cryptosporidium*, *Cystoisospora*, and *Microsporidia* look similar, but the big difference is actually in how we diagnose them. So, *Cystoisospora* and *Microsporidia* won't be detected on a standard multiplex stool PCR, as we've mentioned, and for *Cystoisospora* to directly visualize the oocysts in the stool, the recommended diagnostics include a modified acid-fast stain or UV fluorescence microscopy.

And then for *Microsporidia*, which is much less commonly seen than either cryptosporidiosis or *Cystoisospora*, diagnosis requires either a specialized *Microsporidia* stain of tissue or stool, or a specific *Microsporidia* PCR of the stool. And at my institution, the *Microsporidia* PCR is a send out, as it sounds like it must be for you as well.

Dr. Kalapila

Yes, it is a send out, and the important point about *Microsporidia* testing is that the available diagnostics are primarily designed to detect specific species, such as *Enterocytozoon bieneusi* (or *E. bieneusi*), which is the most common, and the *Encephalitozoon* species, which I probably am mispronouncing that name, but yes. But I think yes, the diagnostics are to detect specific species. And so, a negative test does not necessarily rule out ongoing microsporidiosis. There are other *Microsporidia* species, the details of which I'm just not going to get into, that actually require much more specialized diagnostic testing. And so, it is helpful to involve microbiology colleagues to guide further diagnostic testing if you are very concerned that your patient has a microsporidial infection.

Dr. Budak

That's a great clarification.

preferred-treatment-options**[14:51] Preferred Treatment Options**

Dr. Budak

And so, what about treatment of microsporidiosis? As we've said, ART is the cornerstone for treatment of all three of these OIs.

Dr. Kalapila

Exactly. So, like *Cryptosporidium*, antimicrobial therapy for *Microsporidia* isn't particularly effective without immune reconstitution from ART. Now, you can use agents like nitazoxanide or paromomycin as adjuncts, again, but ART is key, and the main distinguishing feature in microsporidiosis treatment though is that the treatment depends on the specific *Microsporidia* species. So, for example, if it's *E. bieneusi*, the recommended therapies include fumagillin and TNP-470, neither of which are commercially available as oral formulations in the U.S., but they can sometimes be obtained via compassionate care. An alternative is nitazoxanide for 14 days, after which chronic maintenance therapy may be needed. And for *Microsporidia* other than *E. bieneusi*, albendazole can be used for 14 days followed by chronic maintenance for at least three months after ART initiation.

Dr. Budak

Then, in contrast to *Cryptosporidium* and *Microsporidia*, management for *Cystoisospora* relies more heavily on antimicrobial therapy in addition to ART. So, again, separate from, or at least a little bit different than the other two organisms that we've been talking about, the preferred treatment for *Cystoisospora* is trimethoprim-sulfamethoxazole. And then, if a patient is sulfa intolerant, alternatives include pyrimethamine with leucovorin or ciprofloxacin. Treatment is generally 7 to 10 days, and unlike *Cryptosporidium*, chronic maintenance therapy is recommended at lower doses until their sustained immune reconstitution.

Dr. Kalapila

Yes, and fortunately, most of these meds are relatively well tolerated too, without a lot of toxicities or adverse effects.

in-closing**[16:41] In Closing**

Dr. Budak

To wrap things up in the content that we've discussed, the three most common etiologic agents of chronic diarrhea in a person with advanced HIV are *Cryptosporidium*, *Cystoisospora*, and less often *Microsporidia* species. The classic symptoms are a high-volume non-bloody and chronic diarrhea, and severe disease usually occurs when the CD4 cell count is less than 200. Multiplex enteric PCR, if available, can be used to diagnose cryptosporidiosis, otherwise, specialized microbiologic diagnostics are needed for the diagnosis of *Cystoisospora* or *Microsporidia* species.

The most important aspect of treatment for all three is immune reconstitution from ART initiation, which should be started as soon as possible, and antimicrobials are also relied upon for the management of cystoisosporiasis, whereas they are less effective for *Cryptosporidium* and microsporosis. So, with that, we'll see you next time. Aley, thank you.

Dr. Kalapila

Thank you.

credits**[17:40] Credits**

Transcripts and references for this podcast can be found on our website, the National HIV Curriculum at www.hiv.uw.edu. The Health Resources and Services Administration Department of Health & Human Services provided financial support for this podcast. The award provided 100% of total costs and totaled $1,175,136. The contents are those of the author. They may not reflect the policies of HRSA, HHS, or the U.S. government.

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