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IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS): 'WHY IS MY PATIENT GETTING WORSE?'

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Immune Reconstitution Inflammatory Syndrome (IRIS): 'Why Is My Patient Getting Worse?'

[video transcript]

00:00
Our speaker, Dr. James Brust. Dr. Brust is an Associate Professor of Medicine at the Albert Einstein College of Medicine and Infectious Diseases Physician at Montefiore Medical Center. He received his undergraduate and medical degree from Columbia University, and completed both a Residency in Internal Medicine and a Fellowship in Infectious Diseases at the Columbia University Medical Center. He has been at Montefiore/Einstein since 2008, where he attends on the infectious disease consult service and sees patients in the HIV clinic, the Center for Positive Living. He conducts clinical global health research in South Africa with a focus on tuberculosis and TB/HIV coinfection. Since 2012, he has been a member of the New York State AIDS Institute Medical Care Criteria Committee, which publishes guidelines on the management of HIV infected adults. Most recently, in April 2021, Dr. Brust reviewed and updated the New York State Department of Health AIDS Institute Management of IRIS Guideline. He currently chairs the TB section of the NIH CDC IDSA's Guideline for the Management of Opportunistic Infections. So thank you so much, Dr. Brust, for collaborating with CEI to create this new course, and being here to present today. And at this point, I'll let you take it away.

01:28
Thank you, Tara. And thank you to everyone out there in the ether. I long for the days of sitting in a room and getting to see your faces and presenting in person. But hopefully, we'll be able to get something out of today's talk. As Tara mentioned, today's talk is on IRIS, which can be very challenging. It's pretty common, and hard to diagnose definitively, but it's something that just about every HIV provider sees with some regularity.

02:00
So first things first, I have no disclosures, none at all. It's not that I'm withholding them, I truly have nothing to disclose. Today's learning objectives. Hopefully at the end of the hour, you'll be able to define what IRIS is and its characteristic features in patients with HIV. You'll be able to identify patients with HIV who are at increased risk of developing IRIS after starting antiretroviral therapy. You'll be able to determine the optimal time to start ART in patients with HIV and different opportunistic infections. And finally, you'll be able to describe the role of corticosteroids in the prevention and treatment of certain types of IRIS. So this is a rough outline of the talk, I'm going to talk about definitions, talking about how IRIS typically presents and give some general principles of IRIS. And then we're going to spend a decent amount of time about sort of initiation of ART in the setting of opportunistic infections, and drilling down in a bit more detail on three OIs specifically. And then finally, a bit at the end on the management of IRIS, what we can do, and the role of steroids. First, a plug for the New York State Department of Health AIDS Institute Clinical Guidelines Program. As Tara mentioned, I'm a member of the Guidelines Committee, and the website is down in the bottom right. HIVguidelines.org, where we have a number of

guidelines pertaining to the management of HIV, and HIV complications, and the prevention of HIV in adults and adolescents. And this includes one specifically on the management of IRIS, which was updated earlier this year. And much of what I'm going to say today is included in this. So if you don't feel like taking notes, this is freely available to you online.

03:46

So first, what is IRIS? Immune Reconstitution Inflammatory Syndrome, IRIS is an undesirable disease or pathogen specific inflammatory response that may be triggered by ART associated immune system recovery. That's a bit of a mouthful. So the key features here are that it is pathogen specific. It is not just an indiscriminate roaring of the immune system, it is generally focused on a specific pathogen, and it is in the setting of having your immune system recover after starting antiretroviral therapy. And when we speak of IRIS, we generally are talking about two main forms. Paradoxical IRIS, which is sort of the most common one we think of, which is the worsening of a previously diagnosed disease after ART initiation. So you already know you have the disease, as opposed to unmasking IRIS, which is the appearance of a previously undiagnosed disease following ART initiation. So just to be very concrete about that, in paradoxical IRIS the OI is diagnosed before ART, and in unmasking the OI is diagnosed after ART. And most of what we're going to talk about today is paradoxical, but it's important to sort of keep that distinction in mind. IRIS is very protein and because it involves so many different OIs and because it's poorly understood, it can do a lot of things. So usually, these are sort of some key concepts, usually IRIS appears between four and eight weeks after starting or changing antiretroviral therapy, and following an initial improvement in the OI. That said, it can appear later, three months, four months, it's been reported a year out. And it depends on the OI in question, some have a tendency to kind of appear later, KS comes to mind. IRIS is usually mild or moderate. However, cases can be life threatening, and very, very serious, and we'll talk about sort of situations in which that's more common, but generally, it's a nuisance rather than a life threatening condition. IRIS usually appears in patients who have low CD4 count and high viral load at the time of ART initiation. And that makes sense conceptually, that if you are starting from a lower CD4 count, you have more immune recovery possible and the contrast between a state of immune restoration and immune suppression is much more dramatic. That said, it has certainly been reported in patients with high CD4 counts, low viral loads, and even in patients who are HIV negative.

06:20

Incidence rates are hard to measure in IRIS and reading review articles on IRIS can be very frustrating because when they pool together different studies, they'll say IRIS can occur in 2 to 80% of patients, which isn't that helpful, or up to 90% of XYZ. In general, the ballpark figure is about 10 to 15% of patients starting antiretrovirals, in the setting of an OI, will experience IRIS. So that should give you an idea, it's not rare to have some degree of IRIS. Again, usually mild or moderate. And the incidence rates depend on different OIs. CMV IRIS is much more common, for example, than toxo IRIS. The manifestations of IRIS. How IRIS will appear will depend on which OI we're talking about and the location of that OIs disease. So for example, pneumocystis IRIS, there are a couple of chest X rays here in the upper right hand corner, published by Lowe

et al. in 2014. What we're missing here is actually the original chest X ray. So the patient originally had PCP, was treated, did better. The chest X Ray did better. Started antiretroviral therapy, and then one month into antiretroviral therapy comes in with this chest X ray, looking terrible, but they ride it out and then two weeks later, it looks like this. But you can have lymphadenitis, you can have fever, you can have dyspnea. It's usually culture negative. At this point, usually the OI is getting better, it is actually being treated by the OI therapy, and the problem is not antibiotic failure, but immune overactivity. Lots of diseases, most OIs can manifest as IRIS at some point. TB, cryptococcal meningitis, CMV, KS, all shown here. Sometimes the cutaneous manifestations can be prominent, this is less really a paradoxical reaction. It's more a flare or a reactivation. And so you might call it an unmasking IRIS, except that it's sort of hard to categorize that way, but it is quite common early in antiretroviral therapy. There is no test for IRIS, which can be challenging. So it's largely a diagnosis of exclusion, and I'll say more about that at the end of the talk.

08:47
But there are some clues in certain conditions. PML, Progressive Multifocal Leukoencephalopathy, is one example. As many of you know, on MRI, PML lesions don't enhance with contrast, and there is no mass effect. So shown here is acute PML. And here's your lesion, in the white matter, and it has no mass effect. And this is a contrast scan, which shows hardly any contrast enhancement. One month after starting antiretroviral therapy, however, the patient looks like this. And now you see a bowing into the ventricle, bowing of the septum, and on the contrast scan you now see contrast enhancement. Another month later, the mass effect seems to be regressing and there's less contrast enhancement on this side. So that is sort of one helpful imaging clue. But in general, and this is the first main teaching point here of this talk, don't stop the antiretroviral therapy, if at all possible. Sometimes you may not have a choice, but those cases should be really, really unusual. In general, these patients need antiretrovirals, they need immune recovery. And if you stop the anti retrovirals, you're at risk of developing antiretroviral resistance, but also keeping them immune compromised, and they're at risk of developing other OIs. And so pressing through and managing the symptoms as best you can, it should be the goal.

10:12
So we'll start with our first case. A 27 year old man undergoes HIV screening by his primary care doctor. He feels well, he has no complaints complaints. He is unmarried and he has multiple female sexual partners. He admits to occasional intranasal cocaine use and sporadic condom use. He has no other medical problems. He lives alone and works as a superintendent. He takes no chronic medications and his HIV test, a fourth generation antigen antibody test is positive. My first question, when should this patient start antiretroviral therapy? A) today, B) in about two weeks after after he's had a chance to process the diagnosis and demonstrated an ability to come back for follow up appointments, C) depends on a CD4 count, D) when he develops an opportunistic infection, or E) never and he just needs veterinary grade ivermectin. Okay, oh, I love it. This is an informed crowd. Excellent. So the answer is today. Absolutely right. Everyone got it right. All patients with HIV should receive antiretroviral therapy. ART

should generally be started as soon as possible and the same day if at all possible. Does this mean every single person is going to start on the first day? No, but everyone should be offered. And we have guidelines, you see again down at HIVguidelines.org. We have protocols on how to do this. Older providers in the audience will remember the time when this used to be T cell guided, 200, then 350, then 500. But now it's everyone and now it's as soon as possible, and patients don't have to prove themselves by coming to clinic and showing up at appointments and so forth.

11:50

But this was a patient who was sort of just picked up on on routine screening. What if the patient has an opportunistic infection? And so with that, our second case, another 27 year old man presents with three weeks of progressive dry cough and dyspnea when walking, he notices white plaques on his tongue and palate. The chest X ray shows diffuse bilateral interstitial markings and a sputum smear is positive for pneumocystis jirovecii. An ABG shows an A-a gradient of 40 millimeters of mercury. His HIV test is positive, and he has started on trimethoprim sulfamethoxazole and prednisone. Question two, when should this patient start antiretroviral therapy? A) immediately, B) as soon as he's tolerating PJP therapy that's in less than two weeks, C) after completion of PJP therapy in about 21 days, D) depends on the CD4 count or E) never he just needs veterinary grade ivermectin. Okay, most people answering A and a smattering of Bs, Cs and Ds. Fortunately, no one picked E. So the answer here is as soon as he's tolerating PJP therapy. Where does that answer come from? But first, this is sort of the second major teaching point of this talk, for most OIs, patients should start antiretroviral therapy within two weeks, and that includes the ones shown below. The goal should be fairly early, it doesn't have to be the same day. In fact, it's probably a bit overwhelming to start the same day, but this is data driven. And this clinical trial published in 2009, from ACTG Study 5164 by Andrew Zolopa and colleagues, really was the first study to take this on. Back in the day, in fact, when I was a resident, no one knew what to do.

13:38

Everyone was terrified that if you started all these pills at the same time, you would create problems, side effects, and you'd create IRIS and people would die of IRIS, and so it was a sort of a terrifying time. But this study bravely took that on and randomized people to early or delayed ART. And the early arm started in a median of 12 days, the delayed arm waited 45 days. The early arm had less progression to AIDS and less deaths. And this was the breakdown of the OIs in that study. And it's an important limitation of this study. Most of the patients had PJP. Some had cryptococcal meningitis, and very few with CMV or toxo. So it didn't actually look at all those other OIs I told you about. But because of this study, it became standard practice to start antiretroviral therapy early in an OI, within the first two weeks. And we'll say more about cryptococcal meningitis because there weren't enough patients with cryptococcal meningitis in this study to really look at that group specifically. However, we now have tons of clinical experience looking at those other OIs that weren't included in this trial and know that in most cases, people do fine. And in fact, they generally do better.

14:58
Moving on to case three. A 54 year old woman presents with five weeks of productive cough and weight loss. Chest X ray shows a dense right upper lobe infiltrate with possible cavitation. A sputum smear is positive for acid fast bacilli and a GeneXpert MTB/RIF is positive for M tuberculosis, her HIV test is positive. When should this patient start TB therapy? Not antiretroviral therapy, when should they start TB therapy? A) immediately, B) after tolerating antiretroviral therapy and within two weeks, C) after three months of ART or D) it depends on the CD4 count. Okay. Most people say A, some B, some C. Alright. So the answer here is immediately, if you know someone has TB, do not wait. Start TB therapy immediately because TB is going to kill the patient sooner than the HIV.

15:59
Next question, when should this patient then start antiretroviral therapy? A) immediately, B) after tolerating TB therapy and within two weeks, C) after the intensive phase of TB therapy, two months, or after completion of TB therapy in six months, or E) it depends on the CD4 count. Okay, broad response here, 20% A, 43% B, 14% C and 21% E. The answer here is that it depends on the CD4 count. So let me explain. In 2011, the October 20th edition of the New England Journal was a banner issue for people who work in TB/HIV because there was not one, not two, but three randomized clinical trials looking at the timing of starting antiretroviral therapy in patients with pulmonary TB. And it is very rare that three randomised trials show the same thing, but these three had tremendous agreement. Which is that if you have a CD4 count less than 50, there was a mortality benefit to starting antiretroviral therapy within two weeks, within two weeks of starting your TB therapy. If however, your CD4 count was greater than 50, there was no mortality benefit, as long as you started it within eight weeks. The SAPIT Study is down here on the bottom right and was done in South Africa. And that actually had a third arm of waiting until after TB therapy, six months. And that arm was stopped early because of the increased mortality. So you definitely do not wait until TB therapy is over, but depending on the CD4 count, you start within two weeks or eight weeks. The second study here is the ACTG 5221, called the STRIDE study, and this third study up in the upper left is the CAMELIA study which was done in Cambodia. So this is the take home, you start TB treatment immediately, if you have pulmonary TB. And if your CD4 count is less than 50, you start within two weeks. If it's greater than 50, you start within eight weeks.

18:01
But that doesn't say anything about IRIS. So what about TB/IRIS? The first thing to mention is that TB/IRIS is actually one of the best studied forms of IRIS. In 2008, Graeme Meintjes and this group of illustrious TB/HIV researchers published this consensus definition for TB/IRIS. And the goal was really for use in resource limited settings, but it has tremendous utility even in high resource settings. And the idea was that it doesn't depend on lab results and so forth, that it is defined as new or worsening symptoms within three months of starting antiretroviral therapy. And that can be enlarge in lymph nodes, infiltrates, CNS disease or fever. And they really defined the terms unmasking versus paradoxical. And they highlight a few examples of cases they'd seen, large swollen lymph nodes, and then a couple of weeks later the patient develops a

chest wall abscess, and then a couple of weeks later develops the psoas abscess, and all of these when they're drained, they're purulent, highly separative, but they are all culture negative, which is sort of the hallmark of TB/IRIS. So in the SAPIT study, the South African study I mentioned, IRIS was more common when antiretroviral therapy was started earlier and at lower CD4 counts, which is what we sort of said early on in the definitions and common manifestations. And you can see the stratification here, if you look at all the patients, this is IRIS events per 100 person years, early ART was 20.1 versus later ART was 7.7. But when you stratify by CD4 count, the difference becomes way more stark. If your CD4 count is less than 50 the incidence rate was 46.8 events per 100 person years versus 9.9. Whereas those with a CD4 greater than 50, it was a about a two fold difference.

20:00
CAMELIA study didn't stratify by CD4 count, but the median CD4 count in CAMELIA was about 25. So it was a highly highly advanced HIV population, a population with highly advanced HIV. This is a different unit, these are cases per 100 person months, so we can't really compare them to the other table, but you'll see the early ART group in CAMELIA had an incidence rate of 3.76 versus 1.53. That's a hazard ratio of 2.51. And STRIDE, they didn't actually provide it as a longitudinal analysis, but simply reported that 11% of the early ART arm got IRIS versus 5% in the late ART, which is a similar difference, a little more than two. So again, consistent rates of IRIS, more common in early ART and more common with a low CD4 count. However, the mortality benefit overrides the risk associated with IRIS with pulmonary TB.

20:58
Case four, a 61 year old man presents with fever and altered mental status. He's obtunded on exam with nuchal rigidity, the cerebrospinal fluid shows 420 white cells, 85% lymphocytes. The CSF protein is 550 milligrams per deciliter. A GeneXpert MTB/RIF for the CSF is positive for M tuberculosis. His HIV test is positive and his CD4 count is 128. When should this patient start TB therapy? A) immediately, B) after starting antiretroviral therapy within two weeks, C) after three months of antiretroviral therapy, or D) it depends on the CD4 count. Sorry, this is when they should start TB therapy. Good 92% say A. Wonderful. The answer here is immediately. TB meningitis is an emergency, you should start TB therapy if you think it's TB meningitis, let alone if it's confirmed. When should this patient start antiretroviral therapy? A) immediately, B) as soon as he's tolerating TB therapy within two weeks, between two and eight weeks, D) after the intensive phase of TB therapy two months or E) after completion of TB therapy at 12 months. Okay, a spread 41% say B, 36% say C, and 18% say D. And that is great, because the answer here is two to eight weeks, but I put an asterisk because this is not settled science. This is not clear cut and it's definitely a matter of opinion. But I wanted to sort of highlight the debate and what data we have. This is unlike pulmonary TB, where the data is quite clear and the guidelines are all consistent. There is one study examining this and it's a good study. It was a randomized clinical trial by Torok et al., published in Clinical Infectious Diseases now 10 years ago of 253 patients in Vietnam. And if I could just pause for a moment and applaud the people there for enrolling 253 patients with TB meningitis.

23:07

You know, we practice in New York City, and we might see a couple cases a year. 253 is a staggering amount of TB meningitis. The patients in this study were randomized to receive either immediate ART or initiation at two months, the median CD4 count in the trial was 40 cells per cubic millimeter, and there was no difference in nine months mortality. And there were more grade 4 AEs in the immediate arm, 102 versus 87 with a significant p value. So you would say the take home here is that unlike in pulmonary TB, you should not start immediately. That there is clearly something associated with starting early that is higher risk. And the hypothesis is that that's IRIS, that if you start early, that inflammation you see, particularly with low CD4 counts can be very very dangerous when it's in the brain. Inflammation in the lung you can deal with, cough, fever you can deal with, but swelling of the brain can be devastating. However, the guidelines are not entirely sure of how to interpret this. The AIDS ETS CDC IDSA TB guidelines which were published in 2016, take this study at their word and they basically quote. ART is not initiated in the first eight weeks of anti tuberculosis therapy for patients with HIV infection and TB meningitis, even for patients with CD4 counts less than 50. However, the DHHS OI guidelines, and Tara mentioned this on disclosure, I chair the TB section of these guidelines, we were uncomfortable with automatically waiting two months to start antiretrovirals in a patient who needed immune recovery. And we wondered if perhaps the monitoring of patients in resource limited settings might not be quite as acute and intensive as we can offer in high resource settings. And so we write, it is unclear whether these findings are generalizable to higher resource settings, many experts recommend that in people with HIV with TB meningitis, ART should be initiated within the first two to eight weeks after starting anti TB treatment, opting for the first two weeks in those with CD4 counts less than 50 in settings were close monitoring of drug related toxicities and CNS adverse events is feasible. And that's an A3 recommendation, meaning expert opinion. So we acknowledge that we don't have data to defend this. It's really just sort of our nervousness in the idea that if someone does develop IRIS, you could potentially pull back if you can catch it early. But as I say, this is not settled science, and you're certainly on firm ground to wait the two months by other guidelines.

25:47

Moving on to case 5. 61 year old man presents with fever and two to three weeks of progressive headache. He has no nuchal rigidity. He has a normal mental status, his lumbar puncture opening pressure is 50 centimeters of water. The CSF shows two white cells and an India ink stain is positive for Cryptococcus neoformans. His HIV test is positive and his CD4 count is nine. He is started on liposomal amphotericin plus flucytosine. Question seven, when should this patient start antiretroviral therapy? A) immediately, B) as soon as the patient's tolerating AMB and 5-FC within two weeks, C) after five weeks of cryptococcal meningitis therapy or D) at the end of consolidation therapy, which is usually 10 weeks. A spread on this one too, 36% say A, 28% say B, 28% say C, and 8% say D. I like it, things to learn. So the answer here is after five weeks of cryptococcal meningitis therapy. Why? This is the study that drives that. This is called the COAT Trial. It was published in 2014 by David Boulware and Graeme Meintjes. It was a randomized trial of 177 patients conducted in Uganda and South Africa. And they were randomized to ART in one week versus five weeks. One point of note, they were treated with

Amphotericin, not liposomal Amphotericin, but Amphotericin deoxyfolate, and they got fluconazole with it, not flucytosine. Flucytosine is very rarely available in a lot of resource limited settings. And there was a higher mortality in the early ART group, and it was a substantial difference, 45% versus 30%. So what's the take home here? And why is this different than TB meningitis? First, there was an actual mortality difference, it wasn't that there was no difference, there was actual higher mortality in the early ART arm. Now, that said, it's not known in that trial if that's because of IRIS, or if it was just progression of cryptococcal meningitis morbidity, but the take home appeared to be pretty clear that you really shouldn't be starting within a week. And it's hard to make a case to do that. Now, is the right answer three weeks or four weeks? We don't know. We're limited by what they did in the study. And so five weeks is really the standard for cryptococcal meningitis.

28:13
What about toxo though? Some of you should be scratching your head, because I'm sort of drawing the point that CNS IRIS is the most terrifying. And so why did I say early on that it was okay to start antiretroviral therapy within the first two weeks of toxo treatment? And the reason is that toxo IRIS is extremely rare. There have only been a handful of cases reported in the literature, and I don't think anyone really understands why that is. But generally, it's okay to start antiretroviral therapy within two weeks. You should, of course, follow such patients closely. And if they develop any signs of CNS inflammation, you should scan them and be on guard, but it shouldn't stay your hand to start the antiretrovirals early.

29:01
CMV IRIS is actually quite common. And in bunch of prospective studies, the incidence rate was about 37%. And of patients, if you have CMV and then you start antiretroviral therapy, it's very very common to develop some degree of CMV IRIS which the official name is now Immune Recovery Uveitis, although it can be a retinitis or vitritis in its presentation. And it can be sight threatening, and CMV retinitis can be tricky to diagnose, without sort of experience and expertise in a dilated exam. The general recommendation then is don't immediately start ART in someone with known CMV retinitis or strongly suspected CMV retinitis. So if you're seeing someone, a new diagnosis of HIV who's giving you like eye complaints and cloudy vision and maybe you even see signs of retinitis on your exam, you should not start antiretrovirals right then and there. However, just because you didn't see it or suspect it doesn't mean it's not there either. So any patient with a CD4 count less than 100 should be referred to an ophthalmologist for an urgent dilated exam. And if that ophthalmologist sees CMV retinitis, you should have a conversation with that ophthalmologist about whether or not you should stop, progress, keep going with the ART, monitor closely and so forth. There's no good data on this and no trials that I know of examining timing of antiretroviral therapy. Generally, I've seen people propose, you know, two to four weeks of getting CMV therapy. Because remember, again, delaying antiretroviral therapy in someone with a CD4 count less than 100 is in itself very dangerous, because you're keeping them at risk of developing another OI while you're worried about the IRIS.

31:10
So, turning now to sort of more broad questions of diagnosis of IRIS, I've mentioned this before and I'll say it again, there is no test for IRIS. So it is a diagnosis of exclusion. And these are the things you should be considering. First, medication non adherence should be at the top of your list. This is someone who had an opportunistic infection, was on the treatment for that opportunistic infection, and it was getting better and now it's getting worse in the setting of being given more pills. So you need to consider the possibility that they stopped taking their OI treatment. You also need to consider the possibility of drug resistance. This is especially true in TB, where someone might initially improve if you give them an imperfect TB regimen, there might be one or two active drugs in that regimen, but not enough to really suppress, and so they get a little bit better and then they start to get worse again as the resistant clone emerges and is selected. You can consider OI treatment toxicity as well. And you should consider a different OI. These are patients who are generally immune compromised, with advanced immune compromise. So you could be unmasking another OI, or they could have just acquired a new OI in that moment, while their CD4 count was low. But as I said before, you should not stop antiretroviral therapy unless it is severe or life threatening.

32:36
How do we manage IRIS? Well, if it's mild, reassurance is the key. Patients will be very upset, they were feeling fine or they were getting better and you put them on this other medicine and now they're getting worse. And you're nervous. And you need to consider all these other things. And you will probably be starting therapy. You know, someone has PCP for example and they were improving and they get worse now. You don't just immediately say, okay, it's IRIS go home, just continue what you're doing, you probably are starting ceftriaxone azithro, you're keeping them on their Bactrim, you're kind of covering your bases for other things until it just kind of gets better. And that's why a definitive diagnosis of IRIS is usually only sort of made in retrospect, if at all. If they have a cold abscess, often will drain that for sort of comfort and cosmesis. And you can use NSAIDs for kind of inflammatory symptoms. If it's severe, you might consider steroids. So here's the question. Steroids are indicated for which of the following forms of IRIS, A) cryptococcal meningitis, B) Kaposi sarcoma, C) pulmonary TB or D) cutaneous Herpes Simplex. Let's back up. 48% say A, 16% say B, 20% C and 16% D. Good. The answer is pulmonary TB. There is data only in TB. There is data for the treatment of TB IRIS and there is data for the prevention of TB IRIS, and I'll tell you more about that in a second. There is really no role of steroids. Steroids in cyrytococcal meningitis, certainly not in the treatment of cryptococcal meningitis, and that was shown definitively in the CryptoDex trial published in the New England Journal in 2016. In which patients with cryptococcal meningitis were randomized to get dexamethasone upfront the way we do with pneumococcal meningitis and the way we do with TB meningitis. In fact, that study was stopped early because people didn't worse with steroids.

35:10
They had worse cryptococcal meningitis symptoms, more in disability, and it did not prevent IRIS, cryptococcal meningitis IRIS. There was also no role in Kaposi Sarcoma. Steroids are

actually known to worsen the Kaposi Sarcoma, so you should not give it if someone has KS IRIS. Some people will, if they have known cryptococcal meningitis IRIS, that is it's not the acute cryptococcal meningitis, some people have recommended giving steroids if you know it's IRIS and there's signs of sort of cerebral edema, and so forth. Or cryptococcoma, for example, with mass effect, but there is no data to drive that at all. And you should do it with serious caution and in consultation with someone who has done this before and has managed HIV in cryptococcal meningitis. People have used steroids in the symptomatic relief of other forms of IRIS, but there is no data to drive that. It's not quite as contraindicated the way it is in Kaposi Sarcoma, but nor are there trials to support it. This is the trial of the treatment of IRIS, this was done by Graeme Meintjes in South Africa, it was a randomized trial of patients with known paradoxical IRIS, they were randomized to receive prednisone versus placebo for four weeks. The prednisone dose was 1.5 or 1.25 milligrams per kilo for two weeks and then 0.75 milligrams per kilo for two weeks. And that prednisone arm had fewer hospitalizations and fewer therapeutic procedures than the placebo arm and the patients had faster improvement in symptoms and in chest X ray findings. For the prevention of IRIS, Graeme did another study called the Pred ART trial that was published in the New England Journal, just three years ago. This was another RCT, 240 patients at high risk for paradoxical IRIS. So these were patients in South Africa with a median CD4 of 49, who had been started on pulmonary TB treatment, and we're getting better and we're now starting antiretroviral therapy. And they were randomized to receive prednisone or placebo for 28 days and the incidence rate of IRIS in the prednisone arm was significantly lower than that in the placebo arm. Importantly, there was no difference in other infections or KS. There has always been the fear that giving steroids in patients with HIV will cause problems, and they shouldn't be given lightly, but we know that in certain circumstances like in severe PJP pneumonia and in TB meningitis, that when you're treating the OI in question, patients with HIV, even advanced HIV, do okay, especially when it's a limited course of steroids.

38:01
So, the take home points then. You should consider IRIS if a patient deteriorates within the first few months after starting antiretroviral therapy. IRIS is a diagnosis of exclusion, and you should strongly consider medication adherence, problems, and/or drug resistance, as well as a different OI. For most OIs though, antiretroviral therapy should be initiated within two weeks, but the exceptions are pulmonary TB in which it is CD4 driven, TB meningitis where it's definitely not within two weeks and possibly two months, cryptococcal meningitis in which you should wait five weeks, and CMV retinitis where we don't really know the answer, but it definitely shouldn't be immediate. And that steroids can be used to prevent or treat pulmonary TB.

Tara 38:47
We'll just go over a little bit more in detail, just some questions before we jump into our attendee questions. Have some questions for you so you can discuss more about these guidelines. So I just wanted to know if you can discuss more about the different IRIS signs and symptoms of the various underlying OIs, like for example, Hep B and C, mycobacterium avium complex, and TB. Kind of the differences in those visual signs and symptoms.

39:17
Sure, absolutely. I actually thought I was going to run out of time and it's a laundry list of things, and every OI has its own manifestations of IRIS, but there are a couple of key points here. So Hepatitis B and Hepatitis C typically manifest as you'll see them as elevations in LFTs. So you've got a patient known Hep B or Hep C, you start them on antiretrovirals, and their LFTs go up. And that's tricky because you don't know if it was, you know, back in the day when we were using protease inhibitors or NNRTIs, it carried hepatotoxicity risk. You didn't know if it was your efavirenz or if it was IRIS from your Hep B or your Hep C. Nowadays, the antiretrovirals we use are much less hepatotoxic, so you'd be less worried that it's the dolutegravir or bictegravir, for example, than it is IRIS. And you should monitor the LFTs closely, but don't chicken out and stop them, hopefully they'll just sort of come down on their own. For MAI, IRIS is actually kind of an interesting thing in that, I said that most IRIS looks like the OI in question, but that's not actually true for MAI. At least not always. So disseminated MAI is the most sort of common way we think about MAI in people with advanced AIDS, but when they get MAI IRIS, it's more often a focal lymphadenitis. So they get a big swollen cold lymph node in their axilla or in their chest or in their neck, and so that's sort of different. These patients might get fevers and elevations in their Alk Phos and elevations in their transaminases like they did with disseminated MAI, it's harder to make a diagnosis of MAI IRIS, because if you draw the blood cultures at that point you're not going to grow the mycobacterium. Those are probably the most salient examples of other OIs.

Tara 41:18
Okay, great. Thanks so much. And then I did want to ask as well, you did mention CMV retinitis in your presentation. And I know that's one of the updates in April, it was the initiation of ART in patients with CMV retinitis. Could you talk more about that specifically and the change the guideline? I know you might have went over it, but one more time.

41:42
Yeah, no, I think the real issue here is that you shouldn't start antiretroviral therapy immediately. And it's this idea of sort of being very cautious when you're starting someone with a CD4 count less than 100, you need to think of CMV. You need to at least consider it. If the patient gives you ophthalmologic symptoms, you need to look yourself and then hold off on the ART, this is a patient in which you should not start immediately. Remember, our first case was almost all patients should start same day, a potential CMV patient is someone where you should pause. And if their CD4 count is less than 100 and you don't see anything, and the patient's giving you no complaints, that's okay, and you can proceed. But you need to get them to an ophthalmologist soon for confirmation of that.

Tara 42:31
Okay, great. And then one of the other updates in the guideline was the non-use of prednisone for the prevention of IRIS in patients with low CD4 counts. Can you discuss that change in the guideline as well?

42:44
Yeah, I think people used to be a bit more cavalier about prednisone in some ways, and there really isn't data to support as prevention, the only circumstance in which it should be given for prevention is for pulmonary TB. TB meningitis, you're already giving it as part of the therapy. That's not really, I mean, you could say it's prevention of IRIS, but it's sort of considered part of the treatment cocktail for TB meningitis, we know that. It used to be sort of automatic for TB pericarditis, but now no more based on a study out of South Africa a few years ago. So it's really TB meningitis is sort of the only circumstance in which you should be automatically giving prednisone with your TB therapy. And then for prevention of IRIS, it would be pulmonary TB, but there's really no other disease in which you would just give it up front, even if their CD4 count is 2. Start antiretrovirals, and if they get IRIS, deal with it when it comes.

Tara 43:42
Great. Thanks so much for answering those questions. Okay, so now we can get into our questions here, Dr. Brust. So our first question is, hi, Dr. Brust, could you please explain, again, the theory behind ART initiation during active TB based on the CD4 count above or below 50 copies per milliliter?

44:04
Sure, so if your CD4 count, if you have pulmonary TB, remember we're talking just about pulmonary TB, and you have a CD4 count less than 50, you should start your TB therapy immediately. And then within the first two weeks, you should start antiretroviral therapy. So basically, as soon as you like start them on the TB therapy, as long as they are tolerating them well, their LFTs haven't gone through the roof ,and they don't have terrible side effects from the TB meds, you should start your antiretroviral therapy then. If their CD4 count is greater than 50 with no upper limit, it can be 500, 1,000, or 51. You are then allowed to wait until eight weeks. You can still start within three weeks, four weeks, five weeks, and many people do, you just don't want to wait more than eight weeks and you don't have to do it within two weeks. There's no mortality benefit. And if you do it within two weeks, you're probably going to see more IRIS and that could just be a nuisance.

Tara 45:02
Thank you. Our next question we have here, is IRIS associated with any other antiviral meds?

45:11
Not exactly sure what the question is, if you're speaking specifically about HIV meds, there is some suggestion that integrase inhibitors could be associated with IRIS more. Integrase inhibitors, you may know, cause a much more rapid decline in the viral load when you start compared to other antiretrovirals, there's not a lot of difference at the endpoint, you know, all the trials of integrase inhibitors comparing them to NNRTI or PI therapy usually shows similar outcomes at 48 weeks and 96 weeks, but you do see this very rapid drop in the viral load. And

so some people have posited that perhaps that might be associated with more IRIS, if you kind of drop and reconstitute faster. But that hasn't really been shown definitively. And it certainly wouldn't discourage me from giving someone an antiretroviral, you know, based regimen. That may not have been what the person was asking. There are other kinds of IRIS however, there are IRIS transplant patients who stopped their immune suppression can develop IRIS, patients with multiple sclerosis. You know, going on and off meds can develop an IRIS syndrome. I didn't really talk about any of those. And of course, IRIS was really first described in TB and HIV negative patients. Paradoxical reactions are well, well known in HIV negative patients. And it's just sort of the recovery of the immune system. TB itself, pulmonary TB, is a immune suppressive disease. And so when you treat the TB, your immune system comes back and you can develop what looks for all the world like IRIS.

Tara 46:44
Great, thank you. And we have our last question here. For rapid start initiatives, what clinical presentations would make you pause on initiating rapid start? And do you monitor a patient differently if the CD4 count comes back less than 50?

47:01
That's a great question, and not surprising because it's from Dr. Urbina. So there are, I mean, really CMV and CNS disease are the things that kind of give me pause, there's really no other. Like a pneumonia of any kind isn't really going to freak me out. And you have time, right? If you think someone has an OI, then deal with the OI, don't start someone that day. And so the rapid initiation of ART really falls into the box of the patient who's asymptomatic. Right? When we talk about starting someone same day, it's the person who came in, maybe they have thrush, or they were just picked up on screening. And so now you've made your diagnosis, you want to link them to care, you want to get them on antiretrovirals as soon as possible, this is great. But if they're here with pneumonia, I wouldn't start antiretrovirals that day, I would figure out what their pneumonia is. If they have a new abscess in their neck, I would figure out what that abscess is. And I still have two weeks by the guidelines to start antiretrovirals based on what that is. But if they have CNS disease, I might be waiting longer. Or if they have CMV, I might be waiting longer. I'm not sure just having a CD4 count less than 50, if they're completely asymptomatic, and they saw an ophthalmologist who did a dilated exam and there was no CMV, I would not necessarily monitor them more closely. You know, monitoring early into ART tends to be pretty intensive anyway, we want to check labs and check in on them and make sure they're not having side effects from the meds. So I would be bringing someone back in two to four weeks anyway, and telling them to call me if anything happens in the next week, if they get an unmasking IRIS, for example. But broadly, my answer is no, that was a long winded way of saying no.

Tara 48:54
Thank you. And we just got another question in. And it's should I be watching for IRIS in patients being treated with new oral COVID meds?

49:06
New oral COVID meds. Well, no one knows, of course. But I would say, I mean, severe COVID really in itself is an immune disease, right? So it's not so much that you are immune compromised when you get COVID and then your immune system comes back. It's rather you have a normal immune system, and then your immune system goes into overdrive, when you have severe COVID. And that's why, you know, antivirals early in treatment, monoclonal antibodies early in treatment, but if you are severely ill later in treatment, steroids or other immune modulators are probably going to be what helps you. So I wouldn't really think of that in the same lens as HIV IRIS. And an antiviral for COVID is presumably just going to suppress viral replication. But I wouldn't expected it to have a tremendous response on the immune system. If anything, it might dampen what the immune system sees in terms of actual viral replication and viremia.

Tara 50:14
Great, thanks so much for answering all those questions.

50:17
Thank you.

[End Transcript]