Ask The Experts Webinar:
Clinical Conundrums in LTBI Treatment

A National Webinar
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Transcript with times
Beatrice: Ladies and gentlemen, thank you for standing by. Welcome to the Curry International TB Center Ask the Experts Webinar. Clinical Conundrums and LTBI Treatments Webinar. During the presentation, all participants will be in a listen only mode. Afterwards we will conduct a question and answer session.

If you have a question, please press the one followed by the four on your telephone at any time during the presentation. At that time your line will be briefly accessed from the conference to obtain information.

If at any time during the conference you need to reach an operator, please press star zero. As a reminder, this conference is being recorded Tuesday, December 18, 2012.

I would now like to turn the conference over to Jennifer Kanouse, Program Manager at the Curry Center. Please go ahead ma'am.

Jennifer Kanouse: Thank you Beatrice. Good morning everybody and welcome to our webinar. This is Jennifer Kanouse and I'm a Program Manager here at the Curry Center. I'm working with Darlene Clemente, one of our Program Assistants who will be helping us to coordinate today's course.
I have a special announcement, today to hear audio over your computer, you will need to dial in via the phone at this number, 1-800-891-3448. It's posted on your screen. Today we have nearly 1000 participants joining us from across the United States. You should be able to see a seating chart, excuse me -- you should be able to see a seating chart on the lower left hand corner of your screen where each square represents an individual or group.

Excuse me a second. An individual group that have logged in. Today's session is being recorded. We plan to post these recordings on our Web site in the near future for your use. You have been placed on mute in order to preserve the quality of the recording. And for this reason, we ask that you reserve all questions and comments for the Q&A period which will take place after all of our presentations. This webinar is produced by the Curry International TB Center located in San Francisco.

The Curry Center is one of four regional tuberculosis training and medical consultation centers in the country. The Curry Center currently covers jurisdictions in the Western region that include Washington state, Oregon, Idaho, Montana, Wyoming, California, Nevada, Utah, Colorado, Alaska, Hawaii and the U.S. Pacific Island territories.

This project is funded by the Centers for Disease Control and Prevention cooperative agreement and as a collaborative project of
the San Francisco Department of Public Health and the University of California San Francisco.

The webinar is approved for a total of two continuing education contact hours for doctors and nurses. To receive your continuing contact education hours, please login to the webinar and sign the attendance sheet if you are in a group, and complete our online evaluation.

00:03:13 Our course faculty members have indicated that they have not had any financial arrangements or affiliations with commercial sponsors who have direct interest in the subject matter. However, please note that they may be discussing some off-label uses for TB medications.

If your audio disconnects, please call or redial 888-447-1119 for technical assistance.

00:03:44 Okay. Just to get a sense of how many people have logged in, please take a moment to respond to this polling slide and let us know if it's just you or if you're in a group and how many people are in your group.

Okay. Okay.

00:04:28 All right, it looks like we have 154 people logging in saying they're "Just me." And 93 groups of two to five and 12 groups of six to 10. Welcome everybody.
Now I'd like to introduce today's facilitator Lisa Chen. Lisa is the Medical Director at the Curry Center and is a professor in the Pulmonary and Critical Care Division at UCSF. Lisa?

Lisa Chen: Great. Hey, thank you Jennifer. I'm going to just flash to the slide that shows the agenda for today while I talk. I just want to say "Hello, good morning" from the West coast. "Good afternoon” to you guys in the Midwest and the East coast. Thank you for joining our Ask the Expert Webinar today discussing clinical conundrums in latent TB treatment.

So I guess a beginning question is "What do we mean by conundrums?" Well, last year Chris Hahn in Idaho launched the idea.

Basically why not do a webinar that can address some of those lagging issues that come up during treatment for latent TB, particularly those issues where there's no good evidence base and there are no guidelines. So we said of course "Great idea." And that's what we're doing here today.

So, since there aren't guidelines for these issues, we thought the next best thing was really to get together a group of experts, really a great bunch with us today, with years of experience.

Mix it up with both doctors and nursing viewpoints, high incidence, low incidence, settings, urban versus rural -- really program based
experience because what we wanted to do is hear their opinions and primarily tell us how they choose to tackle some of these issues.

Again, we're not proposing any new guidelines. But instead what we want to do is hear best practice advice and really the clinical reasoning behind why they do what they do.

00:06:28 The topics chosen for today, I just want to let you know, really came about through a pretty regional process. And thanks to many of you participating on the call today, when you signed up you sent us really a huge outpouring of potential questions. There was a lot of input and support at the regional advisory committee for Curry, or the advisory group meeting for Curry at the NTCA last summer.

00:06:59 I want to give a special thanks to Jenny Flood and Lisa True and those of you at the California State TB Control Branch who shared with us your top 10 lists of questions. And then finally I want to thank the group who was on our course advisory calls who really narrowed the field to the topics that we're covering today and that would be Heidi Behm and Karen Martinek who are both on the call as faculty,

00:07:28 Chris Jeffris in (correction: Washington) Colorado, Gayle Schack at California State, Masa Narita our Western latent TB expert up in Seattle, King County and then here at Curry, Ann Raftery and James Sederberg.
So for those of you who sent in questions, I just want to let you know that there actually are two things that we're not going to address today, just to be fair. Any questions, and there were a lot, that came in around issues that are readily available in current guidelines won't be addressed specifically today although some of the things may be mentioned.

We will absolutely put on an online set of resources including the guidelines on our Web site for you to link to along with the recording of this webinar so you can have easy access and this includes products from our other regional training and medical consultation centers that address latent TB.

And the second thing, we've also steered away from key questions around interferon gamma release assays, really a topic that's way too big to add to any session.

It's really a session on its own and there certainly will be links to some great webinars even just last year from different centers around that topic.

So let me move on to introduce our faculty, although -- I don't have the picture slide? Oh well, it doesn't matter. I had these great pictures of you all and they're not up here now.

But, from Oregon, we have Heidi Behm who will be doing the first talk who's a TB Controller in Oregon for the last five years. She was an Infection Control Practitioner at Oregon Health and Science
University before that and also worked for five years as a public health nurse in Los Angeles doing nurse case management work.

Calling in from Denver will be Bob Belknap who's an Assistant Professor at the Division of Infectious Diseases at the Denver Public Health and University of Colorado and he works at the Denver Metro TB Clinic with Randall Reves.

Calling in from Alaska is our faculty member Karen Martinek who is a public health nurse with over 34 years of experience doing TB work up there in Alaska. And finally our last speaker today will be Julie Higashi who is the new Director this year of the San Francisco TB Control Unit. She's an Assistant Professor at UCSF here with us in Infectious Disease and for four years before coming to San Francisco was a TB Controller in Santa Clara County.

Everyone on the faculty today have been Curry faculty for years and you may actually get to talk to them someday if you call our Warmline because they're all faculty with us on our consultation line.

So from there let me go on to our first speaker. Heidi Behm, here's her slides popping up. And Heidi's going to be addressing some of the conundrums around screening chest x-rays.

Go ahead.
Heidi Behm: Hi everybody. Thank you for joining today. And thank you to Curry Center for inviting me to be a participant in this. So the first slide I have up here, “The terrain is everything” from Pasteur. So when we're deciding whether or not to get a chest x-ray for somebody, we need to make the assumption of course that they're infected with TB. So you now need to take into consideration what is going on in the body. Is that person immuno-compromised or are they newly infected?

00:11:23 Are they a contact? These factors all play into how likely it is that the person has disease in their lungs and how likely it is that we want to get a chest x-ray for them.

So here are the list of people who are considered to be at higher risk for TB. We really consider these people to be at high risk for breaking down with disease if they're infected. So you can see it's divided into two groups.

00:11:50 We have those who are recently infected, close contacts, immigrants from areas of the world with high rate of TB, kids less than five, groups with high rates of TB transmission such as homeless persons and injection drug users, and people who work or reside with people who are at high risk for TB in facilities.

Second group is immuno-compromised people.

00:12:14 So there again, you see kids less than five, those who are infected with HIV, those who abuse substances, people who have silicosis in
the lungs, diabetes, severe kidney disease, low body weight, organ transplant, head and neck cancer and those who are on medications that suppress the immune system such as corticosteroids or TNF-alpha inhibitors.

00:12:44 So in general, most people only need a chest x-ray when they're newly diagnosed with LTBI or they're -- or prior to starting LTBI treatment, or if they become symptomatic for TB disease. And generally speaking, we don't want to do annual chest x-rays on anybody. We will maybe talk about some exceptions later, but as a general rule, no annual chest x-rays.

So contacts are a whole different situation.

00:13:16 So I would say that contacts to TB cases need a chest x-ray again when they're newly diagnosed with LTBI during the investigation. If somebody is symptomatic for TB disease whether or not the skin test or QuantiFERON is positive or if they were previously diagnosed with LTBI but they're just going to start LTBI treatment now, or if they were previously diagnosed with LTBI either treated or untreated and they're immuno-compromised or less than five years old.

00:13:50 You can see I have an asterisk there that expert opinion may vary in these areas. On the last point, some health departments recommend a chest x-ray for everybody who's previously positive if they're a contact. Other health departments I've noticed might advise a chest x-ray only for those who were previously positive but not treated
for LTBI. So in Oregon we only really give chest x-rays to people who are immuno-compromised or less than five if they were previously diagnosed with LTBI.

00:14:22 And again, at times this may take some judgment on your part. An example is an outbreak we had here at a homeless shelter. We opted to x-ray everybody who was previously positive whether or not they were treated for LTBI. And the reason is of course that this group tends to be malnourished and may have a poorer health status.

So another pretty common question I think is "How old is too old of a chest x-ray?"

00:14:52 So usually if asked this question I say, "If the person is starting or restarting LTBI treatment and they're symptomatic or immuno-compromised or a child less than five, always go ahead and get a new chest x-ray." And again, sometimes expert opinion may vary on this. So for example I would recommend that if the patient you are seeing is HIV positive or on a TNF-alpha inhibitor, you obtain a new chest x-ray prior to starting LTBI treatment even if the last one was just a few months ago.

00:15:29 So this question might be a little bit different if the person was starting or restarting LTBI treatment and they're healthy and older than five. In that situation I would say if the chest x-ray was taken within the last three months, that's an acceptable chest x-ray prior to start of treatment. And again that's an area where expert opinion
varies. So an example might be a healthy health care worker who was TST positive during pre-employment screening. A chest x-ray within the past two months would be adequate prior to starting LTBI treatment.

So just a bit about health care worker screening and chest x-rays, at least in Oregon, this is a really common question. And regulation may vary state by state, so I would advise you call your state TB program for guidance if you have questions about health care worker screening. In Oregon we say that a chest x-ray that's about six months old upon hire is acceptable for purposes of health care worker screening if the person was a prior positive.

However, we are even looking at that again and may make that less stringent in the future.

So just a quick reminder about a couple of special circumstances. If the person is pregnant you want to shield the abdomen. If they're high risk or symptomatic, you certainly want to go ahead and get a chest x-ray right away. If they're not considered high risk you can wait until about 16 weeks into pregnancy before obtaining a chest x-ray.

And then if it's a kiddo less than five years, you want to remember that a PA and a lateral chest x-ray is needed for those guys.

So, thanks again for allowing me to participate today and I look forward to further questions that you may have on this topic.
Lisa Chen: Great, thanks Heidi. I like the little Rudolph look there. So what was great was that in that short time, Heidi really hit a lot of the issues that were raised by many of the questions that we received around this webinar.

00:17:41 I want to let folks know that there's going to be a live question and answer period at the end, after the four speakers. But if you do have questions along the way, we have Ann Raftery here at Curry who is manning I guess, you know, the Q&A chat that's being posted on this webinar but at this point what I really want to do is ask around the table of our faculty and tap them to see how they tackle some of the issues raised by Heidi here around chest x-rays.

00:18:13 So when we talk about the issue, how old is too old in terms of chest x-rays? Julie, from San Francisco: What do you do? What's the practice in your program?

Julie Higashi: It varies depending on the situation and I think you know some of the basic information that Heidi conveyed with a 90-day cutoff, I think that's basically going to be for the majority of our patients, really the timeframe in which we're looking for a chest x-ray.

00:18:46 There are other situations for example with a pregnant woman who comes in before pre-partum where we will accept a chest x-ray if she's got no other health comorbidities up to a year prior to starting LTBI treatment as long as she's asymptomatic. So it really just varies.
Lisa Chen: Well, but those are good examples of times when you would vary the timeframe that you accept and your reasoning -- Bob, do you do anything differently in Denver?

Bob Belknap: Yeah, I think we're really quite similar overall. We sort of have a six-month cutoff for people who are otherwise healthy and have a documented normal film and are asymptomatic. So, I think the examples that were shown for the immuno-compromised or younger children, we have a shorter window of two to three months generally. So fairly similar to what's been described.

Lisa Chen: Great. Well maybe what I'll ask is another question that Heidi brought up. So what did you all do for contacts? Do you get a chest x-ray for everyone or do you break it down much in the way that Heidi had it set up? Julie, let me go back to you.

Julie Higashi: San Francisco, both San Francisco and Santa Clara County where I was before, for contact investigations we routinely get a chest x-ray on everybody regardless of whether or not they've had LTBI treatment previously.

Lisa Chen: All right so that would be the asterisk and "other" category that Heidi had on her slide. How about you Bob, what do you do for contacts?
Bob Belknap: Yeah, for contacts who have previously been positive we will get a chest x-ray as well, you know, regardless of if they've taken prior treatment.

Lisa Chen: And Karen up in Alaska, anything different?

Karen Martinek: Yes. Our experience and practice is a bit different. Our highest incidence areas for TB disease are our Southwest and Northern regions of the state.

00:21:00 We also have very high rates of folks who've been previously exposed to TB. So many, many positive skin tests. We also don't have x-ray capacity and capability in most of those villages and small communities. And so what we do instead for contacts to cases is do symptom screening and collect sputum. Now, of course if individual contacts are symptomatic or if there's something disturbing in the history or physical assessment then they would be flown out to hub communities so that an x-ray could be done.

00:21:39 Lisa Chen: Wow. That would -- flying someone in for an x-ray is a different reality but it does give folks a kind of some of the rationale and thinking behind why you may set your policies the way you do based on the local constraints and what the incidence rate is. Because we've got a full schedule and I'm sure there'll be a lot of questions, I want to just go ahead and move on to our next speaker. Thanks Heidi that was really -- that was great.
Karen -- Karen's slides here, I'll click them up -- is going to be discussing some of the decision-making that happens around choosing latent TB treatment regimens. There were several, several questions submitted to us on this and we will kind of hear from the different programs to see how and why they choose what they choose. But Karen, why don't you go right ahead? Thanks.

Karen Martinek: Okay. Thank you Lisa and thank you everyone for tuning in.

I think this is a topic that's certainly of interest to me and I was delighted to be asked to participate. So, I think first of all just reminding ourselves why we treat latent TB infection and you know, it's rather obvious. We believe that if we treat LTBI that we can prevent the development of active disease and that treating LTBI also saves money because it costs a lot less in terms of drugs and resources to treat LTBI compared to active disease.

So, you know, scratching our heads as we do, sometimes you know, we have to make tough decisions about which regimen. And let's look at some of the things that we might consider when we're making these important choices. And first of all, I think the likelihood of completion, because a regimen that doesn't get completed really is a regimen that doesn't do anyone any good.

Some of the other things that we need to think about when we're making the selection are whether or not the regimens that we're looking at are appropriate for age issues, exposure categories, as well as other issues such as whether or not our infected individual is
HIV positive and also on anti-retrovirals, whether there are comorbidities, whether the patient is pregnant or there might be possible drug interactions.

00:24:15 Social concerns for many of us are huge particularly when we're dealing with folks who are marginally housed, have drug and alcohol issues, mental health issues and so on. And of course drug resistance is also a concern but not one that we will direct -- address directly in this presentation. We will be focusing more on folks who have been exposed to drug susceptible tuberculosis.

00:24:45 So I've compiled this table from the 2000 MMWR just listing all of the possible options. As you know, Isoniazid daily for nine months is the gold standard as you see over here. Some of the other regimens that are also possibilities are intermittent Isoniazid, that is twice weekly usually by DOT.

00:25:18 Regimens take a very long time. A Rifampin regimen of daily dosing for four months, although there are many possible drug interactions. The new kid on the block is this one, the 3HP or Isoniazid and Rifapentine regimen which consists of once weekly dosing of both drugs for a total of 12 doses or three months, but DOT is required. There are also just a couple of other regimens that I put on the list.

00:25:51 One being Rifampin and Pyrazinamide, which is not recommended and there have been fatalities associated with hepatotoxicity. Another regimen which basically is out there but not recommended
in the U.S. is a (correction: three) four-month course of Isoniazid and Rifampin daily.

So again, onto some of the other things to think about when we're trying to make the best decision about which regimen to choose.

Efficacy obviously is a huge issue. Patient preference has a lot to do with whether or not a regimen will be completed. So I certainly encourage you to have some very frank discussions with your patients about what they think they would like to see in terms of a regimen. Side effects, obviously, you must consider. And cost consideration can be considerable for TB programs in jurisdictions.

Not only do drugs cost money but staff costs, particularly those for DOT, monitoring, patient education and of course you can't use intermittent regimens such as biweekly Isoniazid for six or nine months, or the new short course 12 week regimen without DOT. And certainly if DOT access or availability is a problem, then that might limit the choices that you actually do have.

So again, looking at some of this same information in a table, if we look at the gold standard, the INH daily for nine months, we can see that for most of our folks with some of these issues, this regimen would be appropriate. INH biweekly is also something to think about but it can be very expensive because of the DOT.

But both of these regimens actually will work well for most of these factors that I'm suggesting that we consider. The new kid on the
block as I said is the new 12 week short course regimen which consists of Isoniazid and Rifapentine. And again regimen is recommended for children 12 years of age to adults.

00:28:34 It is actually good for folks with social issues because of the DOT it's more likely to be completed.

Another regimen that's popular in some jurisdictions is Rifampin daily for a period of four months and again this would be an appropriate regimen in many cases for children 12 years to adult, folks with INH monoresistance, individuals with some social issues.

00:29:06 Some jurisdictions do use this for children but a six month regimen would be indicated. In this table we're going to look at some of these other factors laid out side by side and I will caution you that in some of these areas and with some of these regimens I had difficulty really finding definitive information.

00:29:37 But again, if we look at efficacy we see that INH daily is extremely efficacious. Biweekly regimen is also similar in efficacy. There is limited information about Rifampin efficacy although it is believed to be similar to six months of Isoniazid.

00:30:07 The new Isoniazid -Rifapentine regimen again has efficacy similar to the nine month Isoniazid regimen.

If we're looking at completion rates, we see that while nine months of Isoniazid is most efficacious, it's also the regimen that's least
likely to be completed. There are poor adherence rates, anywhere from 53 to 76%.

We have much better rates with the Rifampin regimen, daily dosing for four months or the new Isoniazid - Rifapentine regimen that is used for 12 weeks. Rates in the study were up to 82% in completion.

If we look at cost effectiveness, we see that the Isoniazid regimens are actually the least expensive, especially those that are self-administered.

When we get into Rifampin daily for four months, the drug costs are higher, but again self-administered so we don't have DOT costs as we would with the other intermittent regimens including Isoniazid biweekly for six or nine months or the new short course Isoniazid - Rifapentine regimen.

Side effects: Isoniazid-based regimens basically have hepatotoxicity issues in 1-2% of adults which can be significant enough to warrant discontinue of treatment.

Rifampin has fewer hepatotoxic issues but there are other things to consider such as hypersensitivity syndrome as well as orange body fluid. When looking at the new short course Isoniazid - Rifapentine regimen, again side effects will be similar to what we see in the Rifampin and Isoniazid based regimens.
Drug interactions is another consideration and again the regimen with the greatest number of drug interactions would be Rifampin regimens and so you need to think about these things as you're looking at making a good clinical decision about what regimens may be options as well as discussing these things with patients.

I'd like to give you a little information about some of the reasoning behind how we choose treatment regimens in Alaska and of course cost sometimes has a lot to do with it. If you look at daily dosing of Isoniazid either for nine months or six months, these are the most inexpensive regimens that are out there but they're also the ones that are least likely to be completed.

In looking at Rifampin for four months, our drug costs here are considerably higher but we would think about a regimen like this for folks who don't tolerate Isoniazid. When we're looking at intermittent regimens, we see one that we have used often has been nine months of Isoniazid biweekly but our costs are extremely high, $774 for the drug as well as DOT costs.

And that's why we have been early adopters in appropriate areas and appropriate patients for the new short course regimen because we look at dollars and cents as well as likelihood of completion, we see that actually this regimen by DOT is our least costly at $235.

We've experienced -- patients have experienced fewer side effects than with Isoniazid biweekly and completion rates look extremely promising so far.
So, now I'm going to stop talking for a moment and give you guys a chance to respond to a question. If you had a homeless alcohol-using contact to a 4+ smear-positive cavitary TB case, which regimen would you be most likely to choose?

00:35:10 I'll give you another second.

And now I'm going to close the poll and it seems like we have an overwhelming majority who would consider the new short course Isoniazid -Rifapentine regimen. Five percent -- 77%, 5% will think about INH for nine months, 8% would use Rifampin daily for four months and 4% would use Isoniazid biweekly for nine months.

00:35:48 I think our experience in Alaska would go with the majority here. We would probably be most likely to use the Isoniazid -Rifapentine short course regimen. Now another quick question. We have an 11 year old boy in a remote Alaska village. He's a newly infected contact. He's failed a nine month regimen of Isoniazid after only two months. So which regimen do we go to next?

00:36:20 Okay, I don't see the numbers jumping so I will close the polls. And 53% of those who responded recommended the Isoniazid -Rifapentine regimen for three weeks, 29% would try Rifampin daily for four months, 9% you know, actually 14% would go with one of the Isoniazid based biweekly regimens.
And I would say our practice here in Alaska would also be to go with the Isoniazid and Rifapentine regimen for three months.

And one more question for you. With a newly infected, HIV positive pregnant female, which regimen would you be likely to choose?

Okay, and I will close the poll, so vote if you'd like to. Okay. Looks like the overwhelming majority, 70% of those who voted would go with an Isoniazid regimen daily for nine months, 11% mention the Isoniazid -Rifapentine regimen and I would say based on the study and current CDC recommendations, we might want to rethink that.

Because it is at this time not advised for individuals who are pregnant or planning to become pregnant during the regimen. Eight percent would go with biweekly for Isoniazid for nine months or six months and 3% of you chose a Rifampin based regimen.

Some references for you which I'm sure you can print out after.

And at this point I would thank you for responding to my questions, and I suspect that there would be more as well as discussion at this point. Lisa?

Yeah, great. Well Karen there's so many, wow, so many questions we can really talk about and I think a lot of you will probably call in or chat -- use the chat line to raise your own questions here.
But really the decision-making behind deciding what your program will focus as their key latent TB regimen is one that a lot of people grapple with. And let's go straight to our panel and ask folks why -- what have you chosen for your program and why? Let me start with Bob in Denver. What do you do at Denver Metro?

Bob Belknap: Yeah, so we actually made a change a few years ago to Rifampin as our first regimen for latent TB infection.

And the reason behind it was largely related to poor completion rates with INH. So you know, we had been following it for many years and trying different interventions and were unable to get our completion rates really much above the 50% range with nine month INH course and we made the change to Rifampin and we did it somewhat gradually and have been able to get completion rates of 80% with a four month course of Rifampin.

So that really has become our go-to regimen …

Lisa Chen: Those are pretty impressive numbers. And I think for some people that are listening to it may be a surprise that programs have gone completely over to Rifampin but that really is good evidence to it actually working, so, working for you. Heidi, what do you do up in Portland?

Heidi Behm: So INH still remains for most people, although we did expand to Rifampin for contacts.
And we continue to use Rifampin more often and we'll probably start using INH Rifapentine for our high risk contacts starting in January.

Lisa Chen: Great. And Julie, just to compare and contrast, what's happening in San Francisco.

Julie Higashi: Yeah, so San Francisco has for a long time now used Isoniazid for six months for immunocompetent people -- that doesn't include people with HIV or on immune suppression, and also for the folks that need to be DOT'd for their LTBI INH biweekly times six months.

I think that we've stuck with this approach because in another group of our patients who do have abnormal chest x-rays that are stable, we do offer a regimen of INH and Rifampin for four months. And it's possible that with that other option we had a little bit better completion rates. I certainly don't think they're at the 80% rate, but I think that's one of the reasons why our program may have stuck with Isoniazid.

We are now in the phase of really getting our hands all over 3HP or the Rifapentine regimen and it's really, really quite promising as far as tolerability and ease of administration and so we're in the process now of converting over those DOTs that were coming in twice a week on INH to anybody who we can convert over or just offer the
3HP regimen so I really think that this is going to change the way that our program approaches LTBI.

00:42:38 Lisa Chen: Yeah, I think 3HP has a world of possibilities and we're hearing it more and more. I do want to clarify, since you brought up INH and Rifampin option for four months, I think it was a last minute switch to Karen's slides, but actually -- four months of that regimen is something in the fine print of the CDC/ATS/IDSA latent TB guidelines, is an acceptable regimen.

00:43:05 It's the three months INH and Rifampin for latent TB that's not in the U.S. recommendations but can often be seen as the primary regimen in other countries like the UK. So Julie's group uses it often, you said for people with abnormal x-rays that haven't been treated before, so TB4s. And you see the whole variety of six months INH versus nine months INH versus primarily Rif for four months really based on kind of medical risk factors and adherence and your own population data.

00:43:41 Since Julie was mentioning the 3HP, let me just go back to the crowd here, back to the panel and ask, "Are there certain circumstances in your experience with 3HP so far?" Bob, I know you had a great example during our rehearsals that you discussed.

Bob Belknap: Yeah we've been using it on a very limited basis so far but the best example we had was a contact investigation at a local high school where there were a large number of students and faculty who were diagnosed with latent TB infection.
And it was a -- can we consider -- sort of a perfect setting for the use of the once a week regimen because we had a captive audience if you will in a location where we knew we could find them and the opportunity to complete treatment prior to the end of school. So, as opposed to trying to track high school students and teachers into the summer months, we could get through a 12 dose regimen before the end.

And so we had great success with that with -- in that case over 90% completion of the regimen in between 60 and 70 individuals.

Aside from that we've been very selective in our use of it and for us it's largely the DOT that is the challenge, just not having the resources really to do large scale Directly Observed Therapy on patients with LTBI.

We are participating in a study though, through the TB Trials Consortium, that's going to be looking at adherence to the once a week regimen by self-administered therapy. And so we expect -- the study's enrolling now and should take about a year to enroll 1000 patients and so the expectation is that by early 2014, we'll have data on: Can patients adhere to this if you, you know, observe a dose in clinic the day you enroll them.

And give them three more to go home with and instruct them to take it once a week and then follow them up once a month the way we normally do for patients on other LTBI regimens.
Lisa Chen: Well, I should put in a plug that actually Bob Belknap is the study principal investigator for the TB Trials Consortium Study 33 so we're lucky to have him on board today to chat about that a bit.

00:46:19 And really, I -- the added cost for the DOT is really something that's a primary consideration I know for a lot of you folks out there and I think Karen's table that she had on her slides, that really brings home that message that it's going to be harder and harder to afford Directly Observed Therapy for latent TB but certainly there are a lot of social issues and high risk groups where we're looking to really up our completion numbers.

00:46:54 So DOT is our best answer there. And I do want to say as well "Bob, boy, 80 some percent completion rates? Then 90 for the 3HP, they love you guys in Denver, don't they?"

And last but not least, Heidi, how are you looking at 3HP and how are you implementing it up where you are?

Heidi Behm: Sure, so we haven't started using it yet. We plan to start rolling it out at the end of January and mostly just for high risk contacts.

00:47:28 Again, I'm kind of hoping that if their health care worker is going out to do DOT on the case she can maybe also -- he or she can also catch some of the contacts then and do the DOT for them at the same time.
Lisa Chen: That makes a lot of sense. I think -- is anyone else, just -- I know Julie was talking about the INH-Rifampin regimen for four months, anyone else in the crowd who's using that in their programs currently? Bob? Heidi?

00:47:59 Heidi Behm: This is Heidi. Yes, we use it as Julie described for people who have abnormalities on their chest x-rays, TB4s basically.

Bob Belknap: Yeah, we're pretty similar as well. It's folks who we have less confidence that the sputums were, you know, entirely excluded low level active disease and so it serves to treat our own anxiety as much as anything but we do do that when the x-rays are abnormal but stable and cultures are negative and we still have concern.

00:48:36 Lisa Chen: Right, right. I think that's the rationale that I've heard most often as well. And we do know that it's efficacious. So, thanks for your thoughts on all of this and let's go ahead and move on to our next topic. Bob Belknap agreed to tackle some of the common conundrums around management strategies while you're on treatment for latent TB.

00:49:06 And a lot of our questions really came in around "When do you switch regimens?" and "Do you give credits?" and "What do you do about breaks?" So, thank you Bob, for taking this issue on. Go ahead.
Bob Belknap: All right. Yeah, happy to take it on. I was given the opportunity to work on the area that probably has the least amount of data so I was unconstrained by the literature. And so, we're going to go through some challenging scenarios.

And for this it'll be sort of similar to the last talk where there'll be lots of opportunities for the audience to participate. And so for the first case I want to present to you is a 26 year old female who was a recent immigrant from Southeast Asia, had no past medical history, was tested with an interferon gamma release assay that was positive and the chest x-ray was normal. She was started on Isoniazid and came back after a month with complaints of fatigue and headaches and ALT was checked and it was normal.

And the question for folks on the call is "What would you do at this point?" So a month into therapy with headache and fatigue. Your options are stop therapy see if it resolves, encourage the INH but really shoot for six months, encourage INH and try to go -- complete the nine months, switch to Rifampin or switch to once a week therapy. I'll give everyone a few seconds to --

All right, I'll give you five more seconds. All right.

I can't tell if I closed the poll. So it looks like a good mix of people. So most folks would in fact continue the INH and encourage treatment for the full nine months. The next largest group would stop the therapy and see if the symptoms resolve.
And then switch to Rifampin was really third.

What I'd say about this is first that minor complaints are quite common and I'd say more common in fact with Isoniazid than with Rifampin. And for some patients in fact, being able to reassure them that their liver is functioning fine, that they haven't developed any hepatotoxicity and that it's safe to continue will be enough.

I think the important key though is to recognize that even when, in the absence of real objective toxicity, so clear evidence of either hepatotoxicity or hemologic changes, things like that, you need to assess what is the impact on the individual and their sort of daily lives and their ability to function. And for us, this is in fact one of the reasons that we took into account and identified as the problem and the reason we weren't getting folks completed with INH.

And led in part to our decision to switch to Rifampin. And so in this scenario when someone -- when we were using INH as our primary regimen and patients would come back you know a month or two months into therapy complaining of these symptoms and the impact on their lives, we would often switch them to Rifampin. So we had a low threshold to switch people to Rifampin.

So, taking a slightly different approach to the same type of patient, so 26 year old, recent immigrant, no past medical history, positive IGRA and normal x-ray but now comes in after having completed five months of INH and presents with an itching macular papular rash on the arms. So what would folks do in this case? Stop
therapy to see if the symptoms resolve? Treat and encourage INH for one more month, so try to get the patient through six months?

00:53:20 Treat and encourage them to complete the full nine months of INH? Or, switch them to Rifampin?

I'll give you guys about 15 more seconds to go ahead and answer that.

Great.

00:53:49 So most folks actually would stop therapy at that point and see if the rash resolves, others would try to treat the rash and get the person through one more month of therapy, and then a mix of folks would either try to treat through it and continue for the full nine months or switch to Rifampin. So this is another, I think, common complaint is people come in with rashes and it can be difficult to know if the rash is really related to INH especially when you're talking about a nine month course, at some point during the course, the person may develop some skin findings.

00:54:28 Most of these are minor and most of them don't involve systemic symptoms including fever and so there isn't necessarily the concern that this person is going to develop a severe reaction, a Stevens Johnson's or that type severe allergic response. I'd say most often these rashes are something that it's safe and very reasonable to treat through. And so we'll generally treat patients with antihistamines for the itching.
So Benadryl is a common medication that we'll try with folks and then topical agents. So something as simple as a good moisturizing cream, certainly here in Colorado our climate is quite dry and so if patients aren't using good moisturizing cream it will exacerbate even minor rashes. Or mild steroid creams as well. In these settings I would say again, and there's not any right answer to this.

Our approach has been to continue patients and usually we would treat the rash, try to get them through another month and see and if we got that person to six months and the rash was either the same or worsening or was clearly distressful for the individual, we would stop at six months. If the rash got better with our local treatment we would try to continue on to the full nine months. And not unless it was really quite severe or quite limiting in terms of their ability to do their normal daily activities would we stop therapy.

So if it was very severe, we'd stop therapy but short of that we'd try to continue and treat through.

The next case for all of you is an 18 year old male who was born in Somalia and moved to Denver and he came to our clinic with an empty bottle of Rifampin that he had received two months earlier at another health department in the city that he had originally moved to. He came to get a refill so he could continue on therapy and he denied having any symptoms.
But he did say that he had an abnormal chest x-ray, that they had collected sputums on him and the sputums were negative. And we were able to call the health department and confirm all of this by phone and we also confirmed that he had had an HIV test with them and was HIV negative. So what would you do at this point? It's been two months, he feels fine and is coming with an empty bottle of Rifampin.

So your options would be to go ahead and refill the Rifampin, check a chest x-ray on him now, order some labs and let's just say sputum while waiting for the outside records, or switch him to Isoniazid.

Maybe 10 more seconds there. Good.

So it looks like most folks would go ahead and refill the Rifampin. Let me show you what his films look like. So we were able to obtain his x-ray from the outside health department although it took us a week or so I think through the mail, this was before electronic films and things like that. And the x-ray that we got because we did take a film on him.

So the film on the left you can sort of see and I'll put the pointer on it here, there was a left apical fibronodular infiltrate when he was initially seen and as I said, that opacity didn't change over a two month time course when they got sputums. When he came to see us it was much different and had progressed to more of an alveolar infiltrate. So this is a little bit -- gets a little bit back to the first talk on "When do you do an x-ray?"
And in this case, it had been a couple of months and he was asymptomatic but his x-ray had been abnormal. And so, because it was abnormal and it was, you know, abnormal and we weren't able to see it, those were two of the reasons that we repeated the film. And in this case he turned out to have multidrug resistant TB completely unrelated to the Rifampin he received. He was resistant to all first line drugs.

And so, just to highlight an example of where I think if a film is abnormal, then having a low threshold to repeat that film is a good idea.

Case three for you all is a 45 year old homeless male, diabetic and a positive tuberculin skin test. He was prescribed nine months of INH and he completed three months and then came in complaining of nausea and vomiting. ALT was 600 so it's an upper limit of normal in our lab of 40 and he denied any alcohol use.

So the therapy was held for a month and after a month the ALT improved, not quite to normal, but close, down to 76. So your options in this case are you could resume the INH with a goal of completing six months, so he already would be halfway through that, resume INH with a goal of completing nine months, switch to Rifampin for four months, or switch to Rifampin but treat for less than four months, essentially giving some credit for the three months of INH that he had completed.
Looks like most of the votes are in and the majority of people at this point would switch to four months of Rifampin. A few folks would try to restart INH and some would switch to Rifampin but give less than four months. And so I think that in cases where there is evidence of drug induced toxicity, but to a lesser degree.

So, five times normal in this case would be around 200 so if you had an AST or ALT of between 200 and 300 and someone with symptoms and it went away, we certainly have re-challenged some of those patients with INH and done so successfully. So it's not unreasonable to consider that. For us, there's not clear evidence of another cause such as alcohol abuse and it gets to more than 10 times normal, so in our example, over 400 we don't usually re-challenge folks in that case.

But what we do do -- what we would consider is switching to Rifampin and then we would need to decide how much Rifampin do we give? So just a little bit about the durations of treatment and what we know and these are a couple of published reports. The top is from Bulletin of the World Health Organization published in 1982 and this was looking at three different INH durations of therapy.

And you can see that in the top part of that table, of the people who completed three months versus six months versus 12 months, there was very different efficacies in terms of TB prevention with 12 months being the best, 93% effective, and six months being less effective. When they look at, not just the people who completed the
treatment but the intention to treat, so this was looking based on where people were randomized.

Well then the six months and the 12 months becomes much more similar and that gets to the fact that while 12 months is great, the completion rates, the adherence to 12 months of INH therapy is not great and so six months looks very similar to 12 months in that type of an analysis. And it was this sort of data along with the analysis below published by Dr. Comstock that looked at additional data because there were trials that actually looked at giving 18 and even 24 months of INH.

And showed that there really wasn't an additional benefit to giving longer courses. So 24 months looked very similar to 12 months which both looked better than six months. It was obviously recognized that completion of 12 months was poor and that's how we essentially got to the recommendation that nine months of therapy appears to be the best of all worlds in terms of being effective and ideally getting reasonable completion rates.

In terms of Rifampin, we have much less data, although some of the best is the study that is included here out of Hong Kong. And they looked at patients with silicosis and they randomized those patients to Rifampin for three months, Rifampin plus INH for three months, INH for six months or placebo and then followed them up for the development of active tuberculosis. Because this was a high risk population given their silicosis, they actually had a fairly high rate of TB reactivation.
And you can see the three months of Rifampin, three months of INH and Rifampin and six months of INH were all fairly similar and all of them were better than giving placebo. And so the interpretation of these data were that "Well, three months of Rifampin is about the same as six months of INH which we know is probably not as good as nine months of INH." So their recommendation became four months of Rifampin. I will put in a plug for Dick Menses and the folks in Montreal who are in fact studying four months of Rifampin in a prospective randomized clinical trial.

And so we hope to have actual tolerability and efficacy data on this regimen within the next I'd say several years. I don't know exactly where that study is in terms of completing their enrollment.

So how do we interpret this data and how do we use it? So our approach in Denver has been that if a person completes less than three months of INH then -- and we have to switch them for some reason, we switch them to Rifampin and treat them for a full four months.

If someone completes three months of INH though, we figure they're completed a third of their anticipated regimen for INH of a nine month course, so we'll prescribe them three months of Rifampin which is 75% of that regimen, get them through six months of total treatment and consider that adequate. If they've completed between four and five months of Isoniazid well, then
we'll generally give somewhere between two to three months of Rifampin so that they'll have completed a six to eight month course overall.

01:05:44 And then if they've completed six months of INH and then develop tolerability issues, we consider that complete. And so some of it is just, I think the recognition that the person started out with a diagnosis of latent TB infection that wasn't causing them any symptoms. We put them on a drug, Isoniazid, they took it for several months and then developed a problem, became either sick symptomatically or labs were checked and for some reason they had to be switched off of that regimen.

01:06:18 And for reasons of adherence and completion and based on the available data we have, we feel it is reasonable to give partial credit for some of those doses.

So I think the last case I have to show you all is a 34 year old female, foreign born, had recently immigrated to the U.S., has an abnormal chest x-ray with upper lobe fibrosis, has no symptoms but a child at home who is 18 months old.

01:06:49 So sputum are collected and four drug TB treatment is started. At eight weeks, the sputum culture is negative and the chest x-ray is unchanged. And the question for you is "What would you do now?" So stop therapy and consider the patient treated for LTBI? Treat with INH and Rifampin for another two months, so four
months total? Treat with once a week INH/Rifapentine for four months, so get them through a six month course of treatment?

01:07:18 Or switch the person to INH, either INH or Rifampin to complete a standard length course of LTBI so either seven more months of INH or two more months if Rifampin?

I didn't give you guys an option for "Other" so I guess you have to pick the one that is maybe most closely to what you would do in practice. So, it looks like we're all -- most or all of the votes are in and we've got a great mix of what people would do.

01:07:52 So I think the majority would say "Well, we'd switch the person to INH and Rifampin and treat for two more months and get them through four months total." The next largest group would switch the person to either INH or Rifampin and complete a standard LTBI course. And then about 20% said they would consider the person stopped.

And I'll say for us it depends. And it depends on the fact that all fibrosis is not equal and I didn't show you an x-ray at the start of that case.

01:08:22 But here are a couple of examples of patients that we've seen who presented with that scenario. They were tested for one reason or another, they were asymptomatic and had abnormal films. Sputums were culture negative and the films were unchanged after a couple of months. And you can see the film on the left there's a right upper
lobe sort of fibronodular opacity that's relatively minimal certainly compared to the film on the right where you've got volume loss and more dense opacification overall.

01:08:58 And so in the case on the left, I would generally consider that person complete. So while the two month regimen of Rifampin and pyrazidamide is not a recommended regimen because of rare but fatal cases of hepatotoxicity, that regimen did work. It was effective compared to a nine month -- a course of INH for nine months. And so if a person gets through eight weeks of four drug therapy and then we determine they don't have active tuberculosis, we'll consider them complete for LTBI.

01:09:33 In contrast if the x-ray's more abnormal like the one on the right, that is the example where we're a bit more nervous about the possibility of even low level active disease that was not detected by our sputum and our x-rays are not sensitive enough to show changes and so we'll put, oftentimes in that example put the person on INH and Rifampin for another two months, so get them through a four month treatment course.

01:10:04 And that's all I have for you, so I'll stop there.

Lisa Chen: Well, that was pretty darn good, Bob. Thank you so much. You know, it is true, we gave you the hard job of -- well everyone really is -- of answering some of these questions that there isn't data and you know, it's really, really helpful to hear how in a case based way
you work your way through the rationale for why you all do what you do there.

01:10:31 And probably one of the ones I know from people writing in questions to us and discussions with advisory groups, came up a lot is how do you reason through giving partial credit. Now, if you step back a second, I realize -- in some of our discussions leading up to this webinar -- that we really do give partial credit on a regular basis for a lot of our active TB cases and there are times, let's say, even drug resistant cases where you get side effects to drugs.

01:11:03 We have to change the regimen. And we may add time because we know a bit about the efficacy but we don't necessarily reset the clock to zero. But with latent TB, there really is a difference in kind of practice along here, and I know for those of you who are listening who are new to TB care, you're probably scratching your head and going "Yeah, what do they do?"

01:11:28 So having Bob talk about how he kind of looks at the case based on its risk factors for progression and then decides kind of in a proportional way to maybe give credit is helpful in thinking about it. Let me go around the table, the proverbial table since nobody else is here in San Francisco at the Curry Center with me. Julie, over in the clinic in San Francisco, what do you do when you have to switch? Do you give partial credit for treatment already taken?
Julie Higashi: You know, I think I do. And mostly -- and I think the reason why there may be a difference, or my opinion about it, between approach to active TB versus latent TB is just, you're not treating the patient with as many drugs and the stakes, just the difficulty and the toxicity may not be as severe. That being said, many people struggle through latent TB treatment. And so my general practice is if they've gotten through a third of a regimen, then I will really try to include that piece of the regimen and give them credit.

And it's all part of -- I think I like -- going back to Karen she said you know "Your frank discussion with your patients about how they want to move forward. " And you know, when somebody's done their due diligence in taking a few months of a regimen, I really want to value that effort.

Lisa Chen: And, Karen, how would you handle this up in Alaska?

Karen Martinek: Well, in Alaska to date, we have not given partial credit for LTBI treatment regimens when we switch.

You know, if we have to abandon an Isoniazid regimen because of hepatotoxicity, we would usually go to Rifampin for four months daily and do the complete course.

Lisa Chen: In that -- many people will argue that's the cleanest way to handle it because really we are talking about uncharted territory in terms of
partial treatment with one drug and then moving on to partial treatment in the other one.

01:13:44 So there are a lot of folks who would do the same thing that you do there. Heidi, how about in Oregon?

Heidi Behm: Yeah, in Oregon we also have not given partial treatment, or partial credit for treatment, again mostly because we're switching from INH which is a longer course treatment to Rifampin which is shorter so I think as we move more towards Rifampin we might reconsider since, you know, if we would switch from Rifampin to INH, that's longer, so.

Lisa Chen: That's true.

01:14:15 I hadn't even really thought about that if you're starting with INH it usually is, it's usually true, it's usually an advantage switching to Rifampin and my patients will look at me like "Why didn't you offer the shorter one in the first place?" But -- there you have it folks, listening to the different ways of doing it and the reasons why. Certainly this is the art of TB care where there's not a science and a lot of it is very much program based.

01:14:48 A lot of the questions that came in that really pertained to Bob's talk were about breaks in treatment and I do just want to put a plug in for the fact that there are pretty clear general guidance written out there as to how to you know kind of count days and talk about
dosing. So for those of you who may have questions about "What do I do if they've had two weeks break?"

01:15:19 Two months break?" We certainly would direct you to looking at the latent TB treatment guidelines on how to count doses and decide based on the regimen whether or not it's been a significant break in treatment or not and to restart the clock. But during our rehearsals together and our discussions together as a faculty for this webinar, Julie had a question that came up -- and it comes up often actually at least in a clinic here in San Francisco.

01:15:51 Julie, why don't I go ahead and have you go ahead and raise that question about traveling patients?

Julie Higashi: Yeah, sure. So Bob -- and everybody else -- we frequently encounter patients who will be travelling internationally for a significant period of time, both on active and latent TB treatment, but in the cases of those who have already started a regimen and have been on a number of months of treatment and decide that they're going to be away for over a month, how do you handle those lapses, potential lapses in treatment?

01:16:26 Bob Belknap: Yeah, it's -- we run into that as well, more so I'd say with the latents than with the active patients -- and it's a little different I think certainly in terms of the concerns and the risks, but folks who start a latent TB treatment regimen and then they're going to be going on a trip or vacation and gone for two months and they
say "Can't you just give me a two month supply or a three month supply?" And that's, our approach has been not to do that.

01:16:56 You know, we're willing to give a month at a time and that's our standard practice and we'll give people a month if they're going on a trip. And then we'll give them some options. One option would be to try to connect them -- if they're travelling but staying within the United States -- then we offer to connect them with the local health department wherever they'll be travelling so they can go in and get a refill and continue on their medications.

01:17:24 If they're travelling internationally, it's more difficult but we certainly make sure that they have our contact information so that if they -- wherever they go if they're -- if they really are motivated they can have a provider contact us back either by phone or by email. And otherwise we say "Gosh, you know, there really is a window for this." So, you know, if you're taking nine months of INH it's recommended to complete in 12 months, you know six months of INH nine months and four months of Rifampin the recommendation is to complete that within six months.

01:17:56 So there is a window and we'll tell people "Well, here's a month, take it. Yes, you'll be off the medication for a month but come back when you return from your trip and we'll resume and you're not going to have to start over. We'll get you, you know, we'll get you through your treatment course." So that's how we've approached it.
Lisa Chen: All right. Well looking at the time I think it's probably good to move on to our final speaker for today so that we have time for questions and answers at the end.

01:18:25 And so Julie Higashi in San Francisco, she's been willing to tackle some of the questions that come up around latent TB treatment on folks who are also going to be taking TNF-alpha inhibitor treatment. Julie, go right ahead.

Julie Higashi: Thanks and so great to be part of such a wonderful group of faculty and thank you very much for inviting me to participate. I just want to give a nod to Kevin Winthrop who's actually Heidi's medical consultant who is really an authority in this area.

01:18:54 There is an hour-long YouTube video online from a past World TB Day that goes into this subject in depth so I'd recommend anybody who wants more detail to check that out.

Okay. So why is it that this group of biologic agents is so critical in considering when you're looking at a patient as far as risk to progression to TB disease?

01:19:25 And so this slide really, the bottom line is you need TNF-alpha in order to maintain your granulomas. And TNF-alpha works on a number of levels with different cell types. It induces -- it has macrophages produce TNF-alpha to stimulate T-cells and on the other hand T-cells produce TNF-alpha to stimulate macrophages,
and these processes are required to just maintain the structure of the granuloma.

01:19:53 When you get TNF-alpha blockade and so start an anti-TNF-alpha agent, that granuloma is far more likely to break down and cause dissemination of MTB.

So in trying to tackle this conundrum, I'm going to present a clinical case. This is a woman in her 60s, foreign born from a TB endemic country. She has mild to moderate rheumatoid arthritis and has been referred to us by a rheumatologist because she's a candidate for anti TNF-alpha therapy.

01:20:25 And she has a positive QuantiFERON and a chest x-ray with apical fibrosis. We go through a process of getting sputums and showing that her chest x-ray is stable and then offer her latent TB infection treatment. And this particular lady went through a number of regimens, Isoniazid, Rifampin, Rifabutin, Moxifloxacin and each time she came back saying, you know "I feel really itchy." She did not really have a rash that was noted on her physical exam.

01:20:58 And she tended to self-discontinue her regimens after only a few days to weeks of treatment. So, what should happen next? Should we proceed with anti-TNF-alpha therapy? Should we re-challenge with LTBI treatment? Should we be discussing options with the rheumatologist? Should we readdress the treatment plan with the patient? You know, what should we do?
And I'm just going to wait a little bit longer.

Okay. And so as far as proceeding with anti-TNF-alpha therapy I think we've done a good job of establishing that she has TB infection and so we did not feel comfortable proceeding or clearing her for treatment. We felt like we were sort of spinning our wheels with her as far as the treatment regimens and the lack of objective, I guess, rash that we were appreciating.

Although we do have patients who experience a lot of puritis without rash and that's more typical of Rifampin in our experience. And really actually, this is kind of a trick question because we did both, was to discuss options with the rheumatologist in order to understand, you know, where she was with initiating her anti-TNF-alpha treatment and clearly needed to readdress the whole treatment plan with the patient.

And so in preparing to do this patient, I think it's really kind of necessary to understand why we're embarking on this whole treatment plan and to really look at and know what the risk for progression to active TB on anti-TNF-alpha therapy is. And here I am again, I'm citing Kevin Winthrop who recently published a paper that looked at the Kaiser Northern California Database, which is wonderful because I think it is really representative -- represents our region really nicely.

And so the take-home point from this slide really is that looking at the incidence of -- or the crude incidence rate of TB in the general
population over 50 versus the population of rheumatoid arthritis patients on anti-TNF-alpha therapy, you can see clearly here that it's about a 10 fold increase -- a 10 fold increased likelihood that you're going to see active TB in a population on anti-TNF.

01:23:34 So I think you can now say to this lady, "Your likelihood of progression is higher, and it's about 10 fold higher." And then the next piece is and "Why do we want to go forth with treatment for your LTBI?" And so there's one publication which actually addresses whether or not preventive treatment in this situation is effective and it is a study that was published by Gómez-Reino and really looked at the Spanish National Registry of patients who are on anti-TNF-alpha therapy between 2002 and 2006.

01:24:13 And I included this slide because it kind of gives you an idea of what the screening and treatment algorithm was for the study and it also -- the numbers in the red boxes, those are the cases of active TB that developed during this timeframe. So you can see that on all these folks, what should have happened is that they should've had a TST and then -- not just a TST but a boosted TST -- then, if there was a positive skin test, have a chest x-ray performed.

01:24:44 And if there's a chest x-ray, there's offered -- or LTBI diagnosis made -- and offer of INH treatment. And so at each point of the algorithm, there are opportunities for people to fall off the radar and you can see on the side where they did not end up getting offered INH treatment, there were more cases. And in this particular paper
the two cases that are on the right side were folks that were offered INH treatment.

01:25:13 One was considered to have not been properly screened or gone through this algorithm and the other it was felt that they weren't really taking their LTBI treatment properly.

So what this paper also did was to compare the instance rate ratio back to TB in a rheumatoid population on anti TNF-alpha therapy versus the general population before these guidelines were placed and then afterwards. And so this is really the best example I've found that show that a lot of what we're doing in TB programs can be effective and helpful, which is wonderful, because it all makes us feel good.

01:25:50 And so before the guidelines we can see that this ratio was 19, and after guidelines were put in place, if you were 100% compliant, you could reduce that ratio by 10 fold. If you were partially compliant, you know, it makes common sense, the ratio did not come down all the way. And so I think this is the best evidence I can produce right now that the approach, this treatment plan, really is effective and going to, as much as possible, prevent progression to active TB disease.

01:26:27 So a few more things about LTBI screening and anti-TFN alpha therapy as far as screening, I think one of the crucial aspects of screening is going to be looking at a high versus low risk for exposure and being able to make that assessment in your patients.
And so you will be doing this risk assessment. You will always be offering a screening test which is either going to be a skin test or an IGRA, blood test.

But if you have somebody that you have determined to be high risk for TB exposure, for example someone who was foreign born and comes from a TB endemic country, then you're going to want to do, in addition to the screening test, a chest x-ray as well and that is because in this population because the risk for progression is so high, LTBI treatment is appropriate for anyone who has a history of high risk exposure regardless of screening test results.

And so both might have a negative skin test and a negative IGRA, but if you have apical fibrosis that you find on chest x-ray once you've gone through the process that the AFB, the sputums are negative, that chest x-ray is stable, you will really, really want to address treatment for LTBI.

This is another very sort of big table that looks at the spectrum of criteria by country of whether or not to offer LTBI treatment for this group of patients who fall in this risk group and also the different types of LTBI regimen.

And so if you remember what Karen presented, you can see that a number of the regimens she talked about are used to treat these types of patients and so many of them, there is nine months of Isoniazid, four months of Rifampin. In the U.S.A. the recommendation is nine months of Isoniazid. The other very
important sort of question that comes up is "Well, how long do you need to have patients on treatment for LTBI before they can initiate anti-TNF-alpha therapy?"

And you can see on this table that there is a big spectrum of practice and I think that this really is a clinical decision that you need to base on your patient and many of the factors, in particular the urgency of need to start anti-TNF-alpha therapy. Some patients come in a lot of pain and who are suffering and you really want to minimize the time before they need to be on LTBI treatment in order that they get onto their anti-TNF-alpha agent.

So in my practice I generally, I'm most comfortable when I'm able to determine that the person has initiated anti-TNF treatment, they're tolerating it well and that for me is on the order of one to two months. But certainly if there is a sense of urgency, I am quite willing to reduce the time that the person should be on treatment. And in other cases where people are undergoing immunosuppressant treatment for example cancer chemotherapy, I will initiate concurrent therapy.

So it really is based as the clinical decision, it comes with the art of medicine. I just want to make a note as far as what the TB Net is -- and it's sort of a consortium of European groups that came together to determine a guideline for Europe.
Okay, so now I think is a good time to really discuss as a group how long do you recommend treatment for latent TB infection before starting anti-TNF-alpha therapy?

01:30:21 And I'm going to wait for about -- I think we're getting there -- five more seconds. So concurrent intimation of LTBI and anti-TNF-alpha, at least one week of LTBI treatment, at least one month of LTBI treatment or just entire completion of LTBI treatment. And I'm trying to reveal the results. And they are being resistant. Okay.

So for the most part it looks like 50% of you really felt like at least one month of LTBI treatment.

01:30:55 And I think that really is consistent with you know the need to assess whether or not a person is going to be able to tolerate the treatment. Completion, a good number 42% wait to start LTBI -- for the entirety of LTBI treatment which is on the conservative end but certainly within -- as you can see -- the guidelines. And then a few folks said that they would start concurrent treatment for LTBI and anti-TNF-alpha therapy.

01:31:30 And I would say that that is completely reasonable given the situation but if you have the option to wait a little bit I certainly feel that that is a more prudent way to go.

Okay, so a few more comments about rescreening and retreatment. I'm sure this comes up from time to time and then you sort of throw up your hands and say "Okay, what do I do?" And this is in the
context of rescreening if somebody already has a diagnosis of LTBI, I think the majority of patients who do initiate anti-TNF-alpha treatment do actually get treated for LTBI.

01:32:05 But there are a few I think that really haven't been treated. And in those folks I think a yearly symptom review and a chest x-ray if never treated or symptomatic should be considered. So it's one of those few cases which is really -- when Heidi presented "When do you do your chest x-ray" -- I think it may be an exception. I think it may be a nice thing to talk about around the table.

And then the second thing is of course if there's a new exposure to TB, you are going to have to rescreen.

01:32:39 And so as far as retreatment for exposures, I think you really need to consider the type of exposure that your patient has had. And so if there's a close contact with active case and that active case is very likely to be infectious, I would initiate retreatment for LTBI after making sure that the patient, your contact that you're evaluating does not have active TB.

01:33:03 And then your decision to complete a full course of LTBI treatment sort of rests on the rest of the contact investigation, whether or not the index case is infectious, whether they actually are classified with TB, and also the mean status of your patient, but I really would have a low threshold to complete treatment and be conservative in that case.
And so let's bring it back to our lady, our woman in her 60s with mild to moderate rheumatoid arthritis.

01:33:35 You know she really wasn't bothered much by her symptoms when we re-interviewed her and so after a long discussion during which time she really just didn't seem too convinced about the need to really embark on LTBI treatment, we ended up recommending to her rheumatologist to think of other options and didn't feel comfortable clearing her for the anti-TNF-alpha therapy.

01:34:04 And so we're still waiting to see what their decision is together, but I think that if we had to readdress it with her that the course of therapy that we would go for is the 3HP regimen. For two reasons, one is it's a short course. The other reason that it's directly observed and I think with her history of self-d’cing, it would certainly be prudent and also because of the lack of real rash seen with the other regimen.

01:34:37 And I think that's it for me.

Lisa Chen: Thanks Julie. So I think, you know, now that we've listened to these four different speakers and you think about latent TB treatment, we always go "Oh, LTBI, easy, right?" No. We do run into these issues all the time, really judgment calls until there's more clinical data out there.

01:35:08 So it's really helpful to have heard four different folks give us ideas on how they tackle the tough questions that come up even with
something as bread and butter as latent TB treatment. So with TNF-alpha inhibitors, really you know situations where we've got high concern for getting someone through latent TB treatment and I know that because there's not clear definitive guidance and timing, you know, Julie gave a great slide showing all the different country policies around that.

01:35:46 And she talked a little bit about what she does and why she does it. But how about the folks around the table? Karen, what's your experience?

Karen Martinek: Well, I think when we've had this question come up I've found a great resource from the Heartland RTMCC and we have followed the guidelines that Julie laid out and generally get at least a month of treatment on board or try to complete LTBI treatment before starting the anti-TNF-alpha.

01:36:25 Lisa Chen: That's a good shout out and we will have links to some of these products and resources from other centers so our friends in Texas have a great resource for you folks on this. Heidi? What do you do for cases that need both treatment for latent TB and TNF-alpha inhibitor therapy?

Heidi Behm: Yeah, so Dr. Kevin Winthrop, he's our medical consultant in Oregon so I floated this question by him.

01:36:55 And he said that most of the time he will wait until the person's on LTBI treatment for about two weeks before starting the TNF-alpha
inhibitor. And he said mainly, his main priority is just making sure that they're stable on the LTBI regimen.

Lisa Chen: All right. So Kevin Winthrop, the original source, is recommending at least two weeks. And this is one of those situations where you do, you know, there are, I guess, questions about kind of drug tolerance as well so if you can separate a little bit.

01:37:27 It makes some sense that way just so you can tell which drugs are influencing any side effects. Bob, in Denver, how do you think through this?

Bob Belknap: Yeah, our approach has generally been to make sure the person's on for a month and part of that is just that our standard practice when we start someone on LTBI is to give them a month and then follow them up in that timeframe of a month later. So we haven't really prioritized to see people earlier than a month to you know, to expedite things.

01:38:01 I think some of it is shifting a bit and we had discussed when we were preparing for the webinar I think that the use of the TNF-alpha inhibitors in general is changing somewhat so that people may be reaching for them earlier in the disease course. So a person who's maybe not as sick may be considered for this. And in that case I think you know, it may shift the risk benefit a bit to say "Gosh, maybe it does make sense to try to get them through a complete course of LTBI treatment if whatever disease they're going to be starting the drug for is currently not that bad."
When these drugs originally came out I think that the people I was seeing were mostly folks who had failed multiple other things and were on high dose steroids already and were failing and so there was much more urgent need to try and get them on a TNF-alpha inhibitor and so that was sort of the approach we were taking, "Let's try to get them on LTBI treatment for at least a month." So.

Lisa Chen: Right, I remember that. Really the debate in the early days was "How can we -- so many of these people are suffering so much with their arthritis, how can we hold off treatment that will really give them a lot of relief rapidly?"

And it is a changing field that way in terms of the kinds of cases we're seeing. So I have to say, I can really appreciate the practical sense as well in just the resource, you know, clinic resources and number of visits to the clinic. Thinking in general that "Well, geez, a one month supply first is a good way to do it because they're going to come back and get a one month refill and you can give them the green light to start their TNF-alpha treatment."

So I love practical. In -- Julie, when you were talking, you were asking "Well, what do people do in terms of rescreening, is it a time to do -- do people do repeat chest x-rays especially in people who have -- are on these immunomodulators and perhaps haven't been treated?"
01:40:24 You were saying that maybe this is a time to break the rules and really do routine, both symptom and chest x-ray screening results. Anyone from the panel want to comment on that?

Heidi?

Heidi Behm: I have to say that I don't think I've specifically run across that situation before, so I am not really sure. Yeah, I don't know what Dr. Winthrop would recommend.

01:40:54 I'm not sure if he would actually recommend a repeat chest x-ray or just a symptom screen.

Lisa Chen: What Would Kevin Do?

Heidi Behm: [Unintelligible] hope you don't come across it but I'm sure somebody has. I'm sure somebody has.

Lisa Chen: Well, you know, I think now's time, just to make sure we have a chance and we have some amount of time to take questions from the field. You know, I see that there's been a lot that have even popped up while we've all been talking and Ann has answered quite a few of them.

01:41:26 And there's also some great comments as well, people with extra advice. But I'm going to just before we start answering some of these questions, I want to make sure that I hand the mike over to
Jennifer and the operator just to remind you all how you can submit questions or call in with questions. Go ahead Jennifer.

Jennifer Kanouse: Thank you Lisa. If you'd like to ask questions using our online Q&A tool, click "Q&A" up on the top left hand of your screen.

01:41:59 Type in your question and then click "Ask". That will allow Ann Raftery who's moderating our text Q&A questions to see your question. And the Level Three operator, are you with us right now?

Beatrice: Yes I am.

Jennifer Kanouse: Hello. Will you explain to our participants how to make calls?

Beatrice: Certainly, ladies and gentleman if you would like to register a question, please press the one followed by the four on your telephone. You will hear a three tone prompt to acknowledge your request.

01:42:30 Your line will then be accessed from the conference to obtain information. If you question has been answered and you would like to withdraw your registration, please press the one followed by the three. If you're using a speakerphone, please lift your handset before entering your request. And ladies and gentleman, as a reminder, to register for a question press the one, four.
Lisa Chen: All right, thank you very much. I think we're going to open the floor to those of you either writing in questions or calling in questions.

01:43:04 Let me just ask our operator, do we have any call in questions yet?

Beatrice: And we have no questions at this time.

Lisa Chen: Okay. Well we've got lots that are written in so just let me know if someone does call in. So I think our first question that I have here handed over from Ann Raftery. What about three months of INH and Rifampin for latent TB? Is there anyone who would opt to use that?

01:43:33 You know, as I mentioned, there are folks, you know certainly it's country policy in the UK, it's their standard go-to regimen. But let me pose it to our panel. Is there anyone, Bob, Julie, Heidi, Karen, who would feel comfortable using three months of INH and Rifampin?

Bob Belknap: Yeah, this is Bob. I mean, I guess it comes down to what the decision behind that rationale would be.

01:44:07 I mean, comfortable with it? Yes. To a degree, if we look at the data from the Hong Kong study and the patients with silicosis, the three months of INH and Rifampin performed very similar to a six month course of INH or a three month course of Rifampin alone. I think conceptually it's relatively easy to imagine that that three
months of daily INH and Rifampin would likely perform somewhat similar to the once weekly INH Rifapentine as well.

01:44:37 You know, although those haven't been studied head to head and the population for the TBTT study 26 was very different than the silicotic patients. So comfortable, yes. But we've not ever gone to that. I think we, again in patients who we've chosen to use INH and Rifampin the people with class four abnormal x-rays, we've gone for four months. I guess if you could only get three months for some reason because the person was going to be leaving your jurisdiction or leaving the country or something.

01:45:14 And that's the best you could do and you couldn't use the once a week DOT regimen, then yeah, I don't think there's reason to think they wouldn't work, or wouldn't have some efficacy.

Lisa Chen: Right, I think it's -- that Hong Kong data is a piece of hard evidence to show that it does work, it isn't a part of our current national guidelines and I guess I think that's the biggest pause for many people is that it's not in our guidance.

01:45:46 But I think on a -- you know, when you hit the wall in terms of a patient who that is all you can get in then I think Bob, you're, you know, your thoughts there are completely rational. Let me just skip for a minute, because, I do want to bring up -- since Julie's talk was just the last one there was a comment and a reminder from one of the participants out there.
Julie talked about time where you might, even despite negative screening tests meaning a PPD, an IGRA, you might go ahead in someone who's going to become significantly immunocompromised from the TNF-alpha treatment, you might go ahead and get a chest x-ray because they come from a high risk group. The participant wanted to remind us that in fact many of those people may be anergic at the time they get testing and that's another reason to really think about TB risk factors.

Because oftentimes people do come on chronic prednisone, prednisone methotrexate before they're being moved on to TNF-alpha inhibitors so thank you for making that point. It really is important to think about TB risk factors as you look at the cases for treatment.

There is a question about low vitamin D levels as a risk category for breakdown -- and I'm presuming, breakdown from latent TB progressing on to active TB.

Does anyone on the panel begin to consider vitamin D levels when they're looking at the total risk assessment for their patients being screened? Let me just throw this out toward Julie -- any thoughts on -- ?

Julie Higashi: You know it -- yes, it comes -- not "Yes I do this on a routine basis." But yes this is an issue that's been raised before with a lot of providers who do treat TB.
I don't routinely check for vitamin D levels as part of a risk assessment. I think in our clinic, occasionally we will look for vitamin D in our active TB patients, and levels in that group. But you know, it's something I think that deserves some attention but is not -- we don't currently address systematically.

Lisa Chen: All right. Anyone with any -- is anyone out of the panel routinely looking at vitamin D levels?

Heidi Behm: This is Heidi. We don't routinely look at vitamin D levels, especially for LTBI. But we have started to kind of put out there a recommendation of supplementing active TB cases with vitamin D and that's really up to the provider at the county level but we've made it available anyway.

Lisa Chen: Karen? Bob? Either one of you want to comment?

Bob Belknap: Yeah. We've not looked at vitamin D levels either as a risk factor or for supplementation.

It's just -- there's actually a reasonable body of literature on the subject that, unfortunately hasn't really answered the question or it isn't clear that it's something that intervening upon can make a difference, there's a clear association. And so I guess in terms of are there examples where knowing that the person in addition to whatever other risk factor they have for latent TB also has a low vitamin D, whether that would change your decision process.
And whether to treat for latent TB, what you treat them with or how you manage them if they develop side effects and can't complete, we've never really gone there. We haven't done anything.

Lisa Chen: Karen, any comments?

Karen Martinek: No, we have not addressed the vitamin D level, but given our daylight for half of the year, perhaps we should think about it.

Lisa Chen: Absolutely. Absolutely.

Well, you know, there's a really good question that came up that I think I want Bob to go ahead and address since he's been involved in the studies looking at the 3HP, and let me just reiterate for some of you have written questions. I know Ann's answered it, 3HP again stands for the three month regimen of once weekly INH and Rifapentine, so a newer recommendation for latent TB regimen.

But Bob, the question that came up is one that I know you've just in your study protocols and it was "How do you handle a situation where a patient misses a full week" so misses the once weekly dose of INH and Rifapentine, and then they perhaps have a greater than a one week gap in treatment. How are you handling that and what are the current recommendations?

Bob Belknap: Yeah, it's a good question. The way that it was handled as part of the original trial on this is to say that patients were given a window of 16 weeks to complete the 12 doses, the 12
weeks of doses. So there were gaps, some because of adherence, some because of side effects where patients were having tolerability issues and the medications had to be held and then, you know, if it wasn't something that was a measurable objective toxicity, the person might be re-challenged sequentially.

01:51:43 So -- and oftentimes the re-challenges were with the Rifapentine first followed by the Isoniazid and so for either of those examples, as long as the person was still able to complete therapy within 16 weeks then that was considered acceptable. There was also a -- in terms of the number of doses that you need to complete.

01:52:09 So the study was designed to say that as long as patients completed 11 of the 12 doses within 16 weeks then that was considered acceptable. And I can tell you that all -- nearly all, it was a very high proportion of the patients who completed therapy completed all 12 doses. So we have very small numbers of people who completed 11 doses and were considered to have finished.

01:52:35 But that's the, kind of the decisions that have been used and the timeline that's been used for research purposes. You know, I think we obviously, we just don't know how much of a gap is acceptable but we have to decide what we think is reasonable based on what we otherwise know and so that's what's been chosen.

Lisa Chen: And we do know, at least you know the early outcomes using that protocol, so it's, I think, a reasonable first step.
01:53:12 But you know, we're so lucky to have you on this panel. Here's a really timely question and I don't know if your programs are feeling this effect yet, but one participant has asked "How are you all dealing with the current INH shortage?" As I understand there are different companies who are short on the 300 mg size INH.

01:53:42 Are you feeling it yet? Have you got a plan for it? Does anyone want to comment on that one?

Julie Higashi: I -- this is Julie, I can comment. I've taken two calls about this in the last week from outpatient or private providers. I think this is addressing a situation -- or this is probably most relevant to the situation in California, and so it's as Lisa mentioned, I think it's the 300 mg table that is not available right now.

01:54:19 But two of the other makers of Isoniazid and I think one of them is VersaPharm. I forget what the other one is. I think it's -- not Sanofi-Pasteur, that's the pharmaceutical company that doesn't have any Isoniazid, you can still get the 100 mg tablet formulation for Isoniazid. So that's our advice right now to providers who are asking their pharmacies to get them Isoniazid. And my understanding is the hope is that this will clear up in the next two to three weeks.

01:54:53 And so my advice to them was the sort of treatment interruption advice that Bob talked about which is "Well, it's probably not going to be too much of a problem if we can get the drugs back in two to
three weeks because as long as you finish your nine months within 12 months, you're going to be fine.”

Lisa Chen: I have to admit, Julie and I were just in clinic together yesterday afternoon and, when this issue came up and we thankfully also had on board one of our physicians from California State, Neha Shah, who is also a CDC officer.

01:55:31 And she was on top of the information on the shortage so again, I'm sure the California State offices have been fielding a lot of these calls and they're advocating on our behalf. But, there's -- we only have a couple minutes left and I think there's a really good question that's just, because it's a common one, I want to go ahead and throw out there. For the rest of the questions, we will try to answer people's individual questions, we'll get faculty members to send out an answer hopefully within the -- after the New Years.

01:56:08 But the question quickly is "What treatment would you recommend for individuals with chronic Hep C and who are candidates for treatment for their Hep C, would you do latent TB treatment prior to treating the HCV?" Anyone want to tackle this one?

Bob Belknap: Sure, I'll take it one. I actually treat the Hepatitis C patients who are co-infected with HIV here in Denver so it's come up periodically for us.

01:56:42 There's not any evidence that Hepatitis C treatment in and of itself is a risk factor for TB reactivation. So that's the first thing I'd throw
out that the medications, while the interferon therapy does tend to cause bone marrow suppressions, so cell lines all decrease for most folks, white cells, red cells and platelets -- there's not really anything out there that suggests that TB reactivation is more common in these folks.

01:57:18 So I don't think there's an urgency to treat latent TB either -- in the same sense that there is with TNF-alpha blockers and some of the other immunosuppressive agents. And so I think it's, what we've done is to more weigh the other risks and benefits and so if we feel that their liver disease is at this point they're at a better point to try to undergo that therapy, we'll choose that first.

01:57:49 If we think there are other factors, other -- you know, in the example of HIV, if they're more immune compromised with regards to their HIV so TB reactivation is a greater risk then we'll try to treat them for latent TB infection, and again we, because our regimen of choice has become Rifampin and we do use Rifampin in folks who are on Efavirenz based HIV medications, we're sometimes able you know, if things align correctly, we're lucky enough to be able to use Rifampin and treat people for four months.

01:58:25 And we'll do that beforehand. But I think it becomes a really tricky situation when people are up for liver transplants so they're really at the end stage liver disease with cirrhosis and test positive for latent TB. And again, we generally try to use Rifampin when we can, realizing -- and we're even using rifabutin when there's drug-drug
interactions that preclude it. Just, INH is a scary drug I think to use in people who really have cirrhosis.

01:58:55 I've had a person though that didn't tolerate the rifabutin. Their liver disease decompensated and we had to stop it. And we said "Well, this person's going to die without a transplant. You should proceed with the transplant and then we can readdress trying to treat their latent TB post transplant."

Lisa Chen: Great. Well that's pretty sound advice. I think we've run out of time. I want to thank all of our panelists really for a great discussion on these hard issues with something as "straight forward," and I put that in quotes, as latent TB treatment.

01:59:30 I think for those of you who want credits, please stay on the line and Jennifer Kanouse will give us last minute advice on how to get your credit. And thank you all again for joining us. Good bye.

Jennifer Kanouse: Thank you Lisa. This is Jennifer. I'm going to talk to you really quickly about how you get your credits for this session. Please complete our evaluation by January 4th. Those of you who have pre-registered for the webinar, we've emailed you a link to the evaluation or you can find it on the training Web site, the Curry training Web site on the evaluation tab.

02:00:09 Please complete that again by January 4th. Please note that our new address as of January 1st will be 300 Frank Ogawa Plaza, Number 520, Oakland, California, 94612.
You can find us always on the Web at our Curry Center URL and also you can email us at the Web Workshop address listed on this slide. Thank you very, very much for your attention and time today.

02:00:41 And please stay in touch with us and stay online with us and see what we're up to in the new year. And thank you again. Bye-bye.

Beatrice: Ladies and gentlemen that does conclude the conference call for today. We thank you for your participation today and ask that you please disconnect your lines.

[End of recorded material]