# Advanced Concepts in Pediatric TB: TB and HIV

Welcome to the fifth of eight sessions on Advanced Concepts in Pediatrics Tuberculosis, sponsored by the Southeastern National Tuberculosis Center. Today we present Advanced Concepts in Pediatric TB - TB and HIV.

Today's presenter is Dr. Ayesha Mirza. Dr. Mirza is currently an Associate Professor at the University of Florida in Jacksonville. She is also the Medical Director of the University of Florida Center for HIV Aids Research, Education, and Service, US Cares, and Associate Pediatric Program Director. She has been involved in providing care for HIV infected and affected infants, children, and adolescents for the past 20 years.

As faculty for the Florida Caribbean Aids Education and Training Center, she has provided education and technical support to providers across the state of Florida and (audio break) for the past 10 years. She has also served as the principal investigator for the local performance (audio break) for the past three years. In addition to the AAP Committee on Pediatrics Aids, Dr. Mirza has also served on the Pediatric Infectious Diseases Editorial Board since its inception in 2007.

In addition to her active involvement with (audio break) education of residents, fellows, med students, and other health care professionals, her research and clinical interests include HIV Aids, tropical and travel medicine, and immunizations.

I will now turn this over to Dr. Mirza.

Thank you, Karen.

Hopefully everybody can hear me loud and clear. Good afternoon, everyone. We'll go ahead and get started. I have no relevant financial disclosures.

At the end of this session, hopefully, everybody will be able to describe the epidemiology of HIV and TB and their close relationship; recognize the clinical manifestations of TB in HIV infected children and adolescents; discuss the diagnostic work-up when suspecting TB in this group of patients; and briefly discuss the management of TB in HIV infected children and adolescents.

Before we begin our main presentation, let's briefly talk about a case. DL is a four-year-old male, who is a recent adoptee from an orphanage in Africa. Very little is known about his birth history. He did receive the BCG vaccine in Africa. He has an HIV test done on arrival in the United States, which is positive. His viral load is 154,000 copies per milliliter, and the CD4 count is 199 cells per microliter. He also has a PPD placed, which is 19 millimeters and a chest x-ray with prominent hilar and mediastinal lymphadenopathy.

So the questions that arise are: What would be the next steps in his management? What would you start first -- highly active antiretroviral therapy or anti-tubercular treatment? Given his age, what would be the considerations for starting HAART therapy? How would you monitor his treatment? What complications will be anticipated during his treatment? And any thoughts about the history of BCG vaccination in this child?

So, now we'll go ahead and started with the presentation; and hopefully, by the end of the presentation, you will easily be able to answer all these questions. So we'll come back and discuss these once we are done with the main presentation.

Let's talk about the epidemiology of HIV infection in the United States first. And before we talk about the actual numbers, I just want to stress the fact that I think everybody is aware that the epidemiology of HIV and TB share a lot of similarities. The HIV epidemic actually has been a key factor behind the resurgence and the incidence of TB worldwide and in the United States. And HIV has been a pre-eminent risk factor for the development of TB.

There were 9,582 cases of TB reported to the CDC in 2013. This is an incidence of 3 per 100,000 cases. This is the lowest number that has been reported since 1953. HIV status was known for 88% of the 2013 reported cases. Among those with a known result, 9% were reported HIV positive. This is among ages 25 to 44 years.

This is a graph from the CDC, which basically shows HIV coinfection in persons reported with TB in the United States over the last 20 years, from 1993 to 2013. And you can see that the dark pink line over here basically shows the ages 25 to 44. And then the light pink line shows all age groups. And you can see that the numbers continue to decrease.

Talking specifically about pediatric TB cases by HIV status – and this is also over the last almost 20 years, from 1993 to 2011 – the total N is just a little over 19,000 cases. You can see that the information on HIV results are not available for the majority of pediatric TB cases for about – information is only known in about 24% of the cases.

The minimum estimate is 0.9%. That is less than 1% of reported cases include the notice of a positive HIV test result. However, of the subset of cases that include an HIV test result, 3.7% have a positive result. So we don't really have robust numbers of HIV status on reported pediatric TB cases.

Now, important things to note about the epidemiology of HIV infection in pediatric TB – the major risk factor for MTB infection in all children, including those that are HIV infected, is exposure to an adult with TB. The other thing to note is that individuals with HIV infection and latent TB infection are 30 times more likely to progress to TB disease. Also, unlike other opportunistic infections, decreased CD4 cell count is not necessary for increased risk of TB disease. Finally, TB disease in an HIV infected individual constitutes an AIDS defining condition.

Just a couple of words about global TB and HIV. Globally, TB is the leading cause for death among people living with HIV and AIDS. There are two billion people infected with TB; that is, they have latent TB infection. There are 34 million who are infected with HIV globally, and at least one-third of this number also has TB. In sub-Saharan Africa, 80% of people with active TB disease also have HIV. So these are huge numbers.

WHO estimates that HIV prevalence among children with TB is 10% to 60%; this is in moderate to high prevalence countries. And the reason that this range is so big is because, as you can understand, it's very difficult sometimes to make the diagnosis of TB in children because children often have (inaudible) bacillary disease. And also it's often difficult to make a microbiologic diagnosis in children. So that's why the range is so large.

Let's talk about the pathogenesis of TB. This is very complex, and it's still being understood. However, we know that mycobacterium TB and HIV infection actually potentiate one another. So they accelerate the deterioration of immunological function and result in premature death if untreated. Both infections up-regulate the function of macrophages, which produce various cytokines in response to infection.

It has also been suggested that TB patients have a microenvironment that facilitates HIV infection in several different ways. It increases the expression of co-receptors CXCR4 and CCR5 regulated by MTB products; increasing the pro-inflammatory cytokines, especially tumor necrosis factor; and then causing down-regulation of other cytokines.

While tumor necrosis factor production in response to MTB is required for control of bacterial growth, tumor necrosis factor is known to activate HIV replication in macrophages. So this indicates that host immune response, while initiated against one pathogen, may promote the replication of another.

Further, decreased apoptosis, which is programmed cell death of alveolar macrophages, may also facilitate the development of TB in HIV infected individuals. Then you have depletion of CD4 cells by HIV, which facilitates the deactivation of TB. Depletion of CD4 cells in advanced HIV disease also facilitates the development of extra-pulmonary disease.

We know that the CD4 cells play an essential role in the generation of granulomas. This plays an essential role in the control of TB disease. Therefore, it is understandable that when you have a depletion of CD4 cells in advanced HIV disease, this facilitates the reactivation of TB in HIV infected individuals.

Clinical manifestations of TB in HIV infected individuals – general clinical signs and symptoms of TB in HIV infected versus non-infected children can be pretty similar. You can get intermittent fever, failure to thrive, cough. HIV infected children can present similar to non-HIV infected children. Therefore, you have to have a high index of suspicion.

However, HIV infected children are more prone to rapid progression and disease dissemination. All forms of extra-pulmonary TB have been described in HIV infected patients. Therefore, bone and joint TB, TB meningitis, disseminated TB – all may be seen in HIV infected patients.

Atypical features, such as diffuse interstitial disease and multi-lobar infiltrates, may also be seen in HIV infected children. And as I mentioned before, a high index of suspicion is required to diagnose TB in HIV infected children. Further, you may also have coinfection; therefore, you need to be thinking of TB in these patients.

Diagnosis – as with everything else, a thorough medical history and physical examination is required. TB skin tests, interferon gamma release assays, chest radiograph, bacteriologic or histologic evaluation, and nucleic acid amplification tests are increasingly being utilized, even in resource-poor countries, because sometimes making a bacteriologic diagnosis may be difficult.

Each one of these has a role to play in the diagnosis of TB in children. And each one of these often complements the other when making a diagnosis of TB, particularly in those populations where it can be exceedingly difficult sometimes to make this diagnosis.

For a reaction greater than or equal to 5 millimeters is considered positive in an HIV infected individual. A tubercular skin test has poor sensitivity to detect MTB infection in HIV infected children. 50% or less of these children with bacteriologically confirmed TB are skin test positive.

Effective contact investigation of adults with pulmonary TB, particularly those with HIV coinfection, is the most efficient way to identify at-risk children, both HIV infected and non-infected. So this is no different from children who are not HIV infected. Contact investigation remains key with children who are (audio break) as well as (audio break).

IGRAs, or interferon-gamma release assays, require T-cell activity (audio break). Therefore, HIV infection, as well as the degree of immune function, may diminish the utility of these tests. Younger age, HIV infection, and reduced numbers of T-cells also increase the rate of indeterminate Interferon-Gamma Release Assays results. The T-SPOT TB assay has been shown to perform better than both the TST as well as the quantiFERON test in HIV infected children and adults independent of CD4 counts.

All children who are diagnosed with TB should be tested for HIV infection. Annual TB testing is recommended for HIV infected children beginning at 3 to 12 months of age. And then they should be tested annually thereafter for those who test negative.

The recommendations for HIV screening in TB clinics – the CDC recommends HIV screening for all TB patients using the "opt-out" approach, which means that unless patients specifically refuse screening, they should be screened. When you take general consent for gender and medical treatment, they should also have consent for HIV screening unless they specifically refuse.

Routine HIV testing should also be recommended for patients suspected of having TB disease, persons with latent infection, and contacts to TB patients. Rapid HIV tests can be used in these settings.

What about resource-poor settings? CDC actually came up with a new evidence-based screening and diagnostic approach which has been tested in Thailand, Cambodia, and Vietnam, which are areas where TB is endemic. And this has identified 93% of patients with TB in this particular study. And this performed much better than just using a simple – I'll show you on the next slide – just using one simple screen.

So essentially if you look, asking patients about cough, fever, and night sweats detected 93% of people living with HIV AIDS with TB in this study. Asking patients about cough alone detected less than 33% of patients living with HIV AIDS with TB disease. So if you ask patients if they have cough of any duration – for some reason it's not working.

Anyway, this figure represents the steps taken to screen for TB among people living with HIV AIDS and identified those individuals who need further evaluation. Essentially, if people are asked about cough of any duration alone versus asked about cough and fever and night sweats, it increases the yield. So it's better to ask about all the symptoms rather than just ask about cough alone. This seemed to increase the sensitivity rather than just talking about a single symptom.

Let's move on to management, drug treatment, and interactions because this can be very complicated in these individuals. Let's talk about treatment for latent TBI infection first before we talk about treatment for TB disease.

After the exclusion of TB disease, all HIV positive individuals with a positive skin test or IGRA should be treated for latent TB infection. Preferred treatment regimen is INH for nine months. The dose used is 10-15 milligrams per kilogram per day. Liver function tests should be performed for HIV infected children before starting INH. If the compliance with daily treatment cannot be ensured, then twice weekly treatment can be given by directly observed therapy; and this should be strongly considered.

Now, there is an alternate regimen. As probably most of you know of the 12 dose once weekly INH plus Rifapentine by DOT. This has been successful in adults; however, it is not recommended for children aged less than two years. And it is also not recommended for HIV infected children and adults receiving combination antiretroviral therapy.

Now let's talk about treatment for TB disease. Empiric treatment for TB disease using directly-observed therapy should be started in all HIV infected children and infants in whom the diagnosis is strongly suspected and continued until the diagnosis has been confirmed or ruled out. The total recommended treatment duration in uncomplicated pulmonary TB disease is nine months. For extrapulmonary disease involving bones or joints, CNS or disseminated disease, the minimum treatment duration is 12 months.

For HIV infected children, treatment of drug susceptible TB should consist of four drugs: INH, Rifampin, Pyrazinamide, and Ethambutol. After the initial two-month period, the continuation phase treatment using only INH and Rifampin may be continued with thrice weekly therapy via DOT, provided there has been good response and adherence. Once or twice weekly treatment is not recommended in this group because of the high risk of relapse or treatment failure.

In HIV infected children who have minimal disease without significant immune compromise, if they are fully drug susceptible, a three-drug regimen with INH, Rifampin and PZA may be considered for the first two months, followed by INH and Rifampin for seven months. And some experts may even consider using the INH and Rifampin for four months, so doing a total of six months rather than the nine months of treatment.

Injectable aminoglycosides or ethionamide may be considered as the fourth drug in place of Ethambutol in cases of TB meningitis due to superior CFS penetration.

As you can well imagine, treatment is complicated by multiple drug interactions and toxicities. No dosage adjustment is necessary when you use INH alone when latent TB treatment is being done. However, drug levels should be obtained whenever possible. Liver function tests should be monitored before

starting treatment, then at two, four and eight weeks of TB treatment. Beyond two months, liver function tests should be done every two to three months until the end of therapy. When treatment failure is suspected, change the entire drug regimen rather than a single drug alone.

Basically, when you are treating with INH, that is not a problem. The problem arises when you are using Rifampin. So that is when drug interactions become a real problem, and that is when the role of therapeutic drug monitoring really becomes important. So the choice of combination antiretroviral regimens must consider the critical role of Rifampin because of its bactericidal and sterilizing properties.

Rifampin causes potent induction of the CYP3A enzyme system and approximately-glycoprotein-mediated efflux that lowers combination antiretroviral drug levels, especially the protease inhibitors, except Ritonavir which actually partially reduces this effect. There is a moderate reduction also seen with Nevirapine levels. The nucleoside reverse transcriptase inhibitors and Efavirenz levels are least affected.

Rifabutin, which is a rifamycin-class semi-synthetic antibiotic which is related to Rifampin, exhibits minimal CYP3A induction and has been used in place of Rifampin; however, data in children are limited. Rifabutin has fewer drug interactions than Rifampin, but it does require dosage adjustments for the combination antiretroviral drugs.

Besides these medications, other antiretroviral drugs, such as integrase inhibitors and other combination medications, have not been evaluated in children. However, ongoing studies in adults suggest that dosage adjustment may be necessary with these medications as well.

In terms of other medications, such as the CCR5 inhibitors, since these drugs are also metabolized by the cytochrome P-450 isoenzyme system, these also would require dosage adjustments when co-administered with Rifampin. Once again, obtaining drug levels when available and close monitoring for toxicities is essential when administering concomitant combination medications and TB medications.

The most important take-home point is that when you are using combination antiretroviral medications along with TB medications, particularly Rifampin, then basically you need to be able to monitor drug levels because there is a high risk of drug interaction. And particularly when you're using protease inhibitors because pretty much all the drugs have interactions, except for the nucleoside reverse transcriptase inhibitors and Efavirenz. Those are pretty much the only drugs that have the least amount of drug interaction.

Now we can talk about specific regimens that you would use that are recommended for use in these individuals. Concurrent use of combination antiretroviral medications and TB medications – depending on the age of the child, so if the child is less than 3 years or less than 10 kilograms, either to retain or start, if they are on an NRTI backbone, you would retain or start that. And obviously, when you use NRTI backbone medications, you would use at least two. The third drug that you would use would be if the child who is less than three years of age is already on Nevirapine, you would consider either you would switch to Lopinavir/Ritonavir or you would continue with the Nevirapine, which you would use high-dose Nevirapine usually because Nevirapine doses are also reduced. So usually you would go with the higher dose of Nevirapine.

If a child is already on Lopinavir/Ritonavir, then you would adjust the dose of the Ritonavir. Usually you would use what you would call super boosting of Ritonavir. So basically, the Ritonavir dose would be the same as the Lopinavir dose. Or the other option would be you would switch to Nevirapine.

And then if you are starting HAART, the third option would be that you could use a triple NRTI regimen which, in most cases, is not ideally recommended because there is always the risk of treatment failure. And this is only recommended if the viral load is less than 100,000.

So your three options are for the third drug, if you are on Nevirapine, either consider switching to Lopinavir/Ritonavir. If you are on Lopinavir/Ritonavir, adjust the dose of Ritonavir. Or a third option is consider adding a third NRTI if your vital load is less than 100,000.

Now, if the child is greater than 3 years of age or greater than 10 kilograms, then again you have your NRTI backbone. You again have two NRTIs. And then for the choice of the third drug, your first option is if you are on Efavirenz, then you continue on the same dose. The second choice is if the child is on Nevirapine, then either you switch to Efavirenz or you continue Nevirapine but you use high-dose Nevirapine. And your third option is if you are on Lopinavir/Ritonavir, if you can, you switch to Efavirenz.

If the viral load is undetectable and there is no prior NRTI exposure, you continue Lopinavir/Ritonavir; but again, you adjust the dose of Ritonavir so it is equivalent to the dose of Lopinavir. And the third choice is you switch to Nevirapine if you cannot use the previous two options and if the viral load is undetectable and you have no prior NRTI exposure. So you do have your limitations, but there are certain options that are available.

And then the last option would be if you are starting HAART, you do have that option of using a triple NRTI regimen. Again, this is the least favorable option you have; and you only would use it if the viral load is less than 100,000 because, again, there is always the chance that you could fail this regimen.

There are some special considerations for HIV infected patients. The first one is the risk of immune reconstitution inflammatory syndrome or what we call the IRIS. TB associated IRIS may occur after the initiation of anti-tubercular therapy. It may present with new onset symptoms such as high fever, worsening adenopathy, pulmonary infiltrates. Essentially, it may appear clinically as if the individual who has TB, it may appear as if the TB suddenly seems to be getting worse. So the patient is not getting better; the patient is actually getting worse.

It is more likely to occur in those with advanced immunosuppression. It should be suspected when there is exacerbation of symptoms, and this may develop within three to six months or sooner of initiating combination antiretroviral therapy.

This may occur in the setting of presence of TB in the host prior to the initiation of cART -- that's the first condition – or there is actually a paradoxical worsening of TB in TB-HIV co-infected patients. Mild to moderate symptoms of IRIS can simply be treated with non-steroidal anti-inflammatory agents, or short-term use of systematic steroids may be considered in severe cases. Usually treatment for TB and combination antiretroviral therapy should not be discontinued in these individuals.

The next question which often comes up is when to start treatment. For children who are not yet receiving antiretroviral therapy, when is the best time to start treatment? Early treatment, preferably within two to eight weeks of starting anti-tubercular treatment, should be planned. We know from results of studies in both adults and children that early initiation of HAART, within two to eight weeks of starting anti-tubercular therapy, has been associated with a significant reduction in mortality.

Children with advanced disease may need to start HAART treatment even earlier – earlier meaning starting at two weeks rather than eight weeks of treatment. So start anti-tubercular therapy right away, and then start HAART therapy as soon as possible, as early as two up to eight weeks after starting anti-tubercular therapy.

As far as management of HIV infected persons who are contacts to active cases, initial evaluation – which would be the tuberculin skin test or the interferon gammon release assays, chest x-ray, symptom review and physical exam – if all of the above are negative, then they should be treated as latent TB infection with INH for nine months.

What about the risk of recurrent disease? Re-infection disease should be managed the same as first-time TB. Secondary post-treatment prophylaxis is usually not recommended. However, regular TB exposure screening should be continued after completion of treatment; and preventive therapy should be considered whenever repeat exposure occurs. So once you complete treatment, there is no need to do secondary prophylaxis and follow-up screening should be continued.

In terms of relapse and recurrent disease, TB recurrence can represent relapse or re-infection. The relapse rate is low in children with drug susceptible TB who receive both DOT as well as combination antiretroviral therapy. Recurrence within 6 to 12 months of treatment completion should be regarded as relapse and managed the same as treatment failure.

If you have a recurrence which is greater than 6 to 12 months post treatment, this is probably re-infection disease, especially after new TB exposure or there has been a visit to a TB endemic setting. So it's not considered a relapse but probably a recurrence of a new episode of disease.

Let's go back now to our case discussion. Hopefully, we covered most of our questions during our discussion. Just to refresh our memory, our patient was a four-year-old male who was a recent adoptee from an orphanage in Africa. Very little was known about the birth history. He did receive the BCG vaccine in Africa. And he had an HIV test done on arrival, with a viral load of 154,000 and a CD4 count of 199. He also had a PPD placed, which was 19 millimeters, and a chest x-ray with prominent hilar and mediastinal lymphadenopathy.

The first question was: What was the next step in the management of this patient?

Clearly from the chest x-ray, it was very obvious that he had pulmonary TB. So because the patient is four years old, it would be unlikely that he would be able to expectorate and give us good sputum samples. So likely, the patient would need to be admitted for gastric aspirus so that we could get some samples and be able to make a microbiologic diagnosis. So he should be admitted for gastric aspirus so we could get ASC samples for smears and cultures.

We should also get baseline liver function tests, CDC, ESR because we will be anticipating that we would need to start treatment on him. Given that he is also HIV infected and we would anticipate that we would need to start HIV treatment on him sooner rather than later, I would also do an HIV genotype on him. And then given that we know he has TB, I would anticipate starting anti-tubercular treatment.

The next step would be, once we have done the baseline tests on him, obtained the three gastric aspirates on three separate days and obtained the baseline tests, start him on a four-drug treatment. So the next step would be start him on HAART first or start him on anti-tubercular treatment. I would start him on anti-tubercular treatment, which would be the INH, Rifampin, PZA, and Ethambutol.

He is four years old, and we have tried sometimes in the children's hospital to get our ophthalmologist to do an eye exam. But sometimes it's very difficult at that age. Children don't always cooperate, so it's not always easy to get a good baseline eye exam. But at that age also to start them on aminoglycosides means that you have to put in a PICC line, so that sometimes is not always practically possible. So I would still put him on Ethambutol and still just monitor him very carefully.

Start him on four-drug therapy and then basically once his treatment is started after that, probably if he is doing well at any time two to eight weeks later, start him on HAART therapy. And of course, once he gets started on anti-tubercular therapy, he would need careful monitoring of his liver function tests. And so we would follow the algorithm that we talked about, which would be that the liver function test would need to be followed at two, four, and eight weeks; and then if we went beyond two months, then basically every two to three months until the end of treatment.

And then in terms of HAART therapy, what would the options be? Once we get the genotype back, and if he does not have any mutations, specifically for him if he does not have the 184 (inaudible), then given that he is four years old, the best option would be to start him on Efavirenz. That would be my first option for him.

And then how would we monitor his treatment? Essentially, I talked about liver function tests. Given that we also put him on Ethambutol, I would be following him. Obviously, he would be on directly-observed therapy. He would be coming to clinic, and we would be doing careful exams on him making sure that he

did not have any vision complaints. Probably we would be checking when we do his blood tests, maybe doing, monitoring his CDC, making sure he is not having any other complaints.

Also I forgot to mention, we'll also be putting him not just on – when we start him on anti-tuberculin therapy, we'll also be starting him on B6 because also we are going to start him on INH. So that would also be an important consideration.

What other complications would be anticipated during his treatment? Apart from monitoring his liver function tests and monitoring him for any ocular toxicity or given the fact that his CD4 count is 199, it would be important in this patient to make sure that he has no issues related to immune reconstitution syndrome because his CD4 count is really low. So that would be something important to watch in this patient.

Also, he is coming from Africa. He is an international adoptee. So as a baseline, it would also be important to make sure that he has no other opportunistic infections. You know, make sure you also look at his other – and this would be something that you would also do as a baseline – look at his other hepatitis serology, make sure he has no diarrhea, no other underlying – his nutritional status is good. So that would be part of his initial management.

And then finally, I just threw in any thoughts about the history of BCG vaccinations; and that is because he is coming from a developing country where BCG is usually given at birth. Now, BCG vaccination is generally not recommended in HIV infected individuals. It is not given in the United States, which is really not a consideration here; but given that the child is an international adoptee, WHO does not recommend giving BCG vaccine to children who are known to be infected with HIV. However, in settings where limited resources are available, BCG vaccine is given at birth to infants, regardless of HIV exposure, given that there is a high incidence of TB in populations with high HIV prevalence.

So basically, what happens is that (inaudible) infants known to be from HIV infected mothers and who receive BCG at birth is recommended. So in this case, basically given that he received BCG, one would disregard the history of BCG vaccination, which is what we do in non-HIV infected children also, when we see that the children who are not HIV infected and they have all the (inaudible), we disregard the history of BCG vaccination. One would do the same in this case.

Clearly, the high adenopathy, the positive PPD is not because of the BCG vaccination. In fact, it is interesting that he has mounted such a big response given that clearly he has depletion of CD4 cells, which is really what is responsible for the positive (inaudible).

With that, I don't know if Dr. Alvarez – who I think is moderating the session – is on the call. So I'm going to see if there are any questions or any comments. And I'm going to turn it over to her and see if anybody had anything else to add.

Thank you, Ayesha. Can you hear me?

Yes, I can hear you.

Great, I am on the call. And we got a few questions, so I am going to try to summarize these for you. The first question is regarding the screening for TB in children. The person's question is: Is IGRA now used as a screening method in children less than five years? Is that acceptable?

IGRA is still not used in children less than five years to my knowledge. I think, people are probably beginning to use it more. I think we are getting more and more information. But I think we still have a greater degree of comfort using TST in children less than five years of age, although definitely we are using IGRA more, especially I think in a situation where somebody may not come back for a TST reading.

Yes, I agree with you. I think we still prefer – in less than five years of age, we prefer TST. However, in certain circumstances, still sometimes IGRA is done and we accept that. But, it's not the preferred test.

And especially I think as we talked about earlier in the HIV infected population because we are depending on the degree of immunosuppression because we are depending on the CD4, with IGRA, you may not get readings, that makes it even less reliable.

Yes, and related to that – the last issue that you just mentioned – one of the person's is asking if you have the study or the reference that showed that the TSPOT TB assay has been shown to perform better than quantiFERON test in HIV infected patients. I think you mentioned that in your talk, so they are asking if you have the reference for that. Now, if you don't have it handy, we could always get the caller's e-mail and then try to e-mail it back to them. But I don't know if you have it handy.

We'll get it and we can send it to them.

Yes, I think we're going to go through the e-mail. If the person that asked that question can send us the e-mail, we can certainly answer the question on e-mail.

The next question is: Since Ritonavir and Lopinavir is a fixed combination adjusting the dose of Ritonavir when necessary and adjusting the dose of Lopinavir as well. Could you clarify?

That is a fixed combination so what you do is you would have to give extra Ritonavir.

So the question is, if you give extra Ritonavir, do you still have to adjust the Lopinavir dose?

You don't have to adjust the Lopinavir. You just have to increase the dose of the Ritonavir to the Lopinavir.

Okay.

So the Lopinavir dose remains the same. It's just the Ritonavir you increase to equal the Lopinavir. Is that clear? I hope.

Okay, perfect. Another question is: When would you send therapeutic drug monitoring (audio break) and the other thing is (audio break).

Okay, so ideally with HIV infection, you are treating someone with a Rifampin-based regimen and you are using combination antiretroviral therapy, the ideal situation would be that you would use therapeutic drug monitoring. And especially, we talked about these medications. Now, imagine if you had someone be very low CD4 (audio break) or they may be on some other medications, the picture may be even more complicated. (audio break). So with a multiple drug situation, you really ideally should use (audio break) monitoring.

(audio break) centers would be helpful in providing you a resource. I can tell you that we have at the University of Florida in Gainesville, Dr. Charles (audio break) they provide monitoring for drug levels. So that is one lab that I know of in the northeastern region that does actually require drug monitoring. (audio break) local TB center would be a good resource in that situation. You can always get in contact with them, and they can probably put you in touch with doing this locally or regionally.

Okay, I think that's exactly what I would say. Get help through the health department; and then if the health department is from the regional TB center to see where is the best place. And as you said (audio break) and we could also always e-mail them that information if they send the question through e-mail.

One more question: What is the difference between treating HIV-1 and HIV-2 in the recommendations for the regimen?

I'm not aware that there are. I think you would still need to use therapeutic drug monitoring, depending on what drugs you are using. You would need to know the susceptibilities of the drugs you are using.

Yes, I agree. I think it's basically individualized; but in general, it's about the same.

Yeah.

There's one more question—

And you would also, I think, need to know – it would be ideal to also know not just the susceptibility. You would need to know the TB's drug susceptibilities, and you would also ideally need to know drug levels. So on both sides, you would need to know what you are treating on both ends.

Yes, absolutely. And the final question -- I don't know that this is related to what your discussion was, but just in case -- the person is asking about the use of gene experts for the susceptibility.

So what's the specific question?

Yeah, I don't understand exactly what the question is about that. So I'm going to ask that person to maybe e-mail us the exact question, and then we can respond back.

We're really right at the end of our time. I think that anybody else that has any more questions, I encourage you to send us an e-mail; and we'll be happy to answer your questions that way.

I want to remind you that you will receive a survey in 24 or 48 hours for evaluation of this activity. And I would really appreciate and encourage all of the participants to answer the evaluation survey that you will receive via e-mail. If you participated in this as a group, you can share the e-mail with the evaluation survey to all the participants in your local situation.

And then I encourage you to join us in the next webinar, which is next month.

Emily, do you have anything else to say?

No, that's it. The next one will be Thursday, February 12, 2015, at 12:00 p.m.

Okay, thank you very much, Dr. Mirza.

Thank you very much, everyone.

Thank you, Dr. Mirza.

Thank you.