

Medical Management of Tuberculosis

Audio Transcript

SLIDE 1 TITLE

[Voiceover]

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An online slide-show and audio presentation for healthcare professionals

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[SLIDE 2] INTRODUCTION

Hi. I'm Dr. Karen Smith. I currently work as Public Health Officer for Napa County, California. I previously worked as the TB Controller for Santa Clara County. I also have a long history with the California TB Controllers Association, and served a term as the organization's president.

For the next thirty minutes, I'm going to be speaking about the basic principles in the medical management of tuberculosis cases, the role that each of the four basic tuberculosis drugs plays in the treatment of TB, and the most common adverse reactions associated with those drugs.

The point of this talk is to provide what I consider the basic information that every nurse case- managing a TB patient must understand. While case managers are the primary audience, others interested in a broad overview of the key principles may also find it useful.

If you understand these issues, you will increase the likelihood the patient is going to be treated appropriately and get through therapy successfully. Unfortunately, we don't have time to go into detail about many of the important issues such as the treatment of multi-drug resistant disease. Instead, we will focus on the basics that all people who either do TB case management or oversee case managers need to know.

[SLIDE 3] CONTENTS

We will cover some of the essential general principles of TB care. We'll talk about the individual drugs that are most commonly used, the basic regimens, a little bit on alternative regimens, a bit on drug resistant and extrapulmonary TB, then adverse reactions, and monitoring. There isn't enough time to cover all these issues in detail, but we will at least touch on each of them.

[SLIDE 4] GENERAL PRINCIPLES

Because *Mycobacterium tuberculosis* is able to rapidly develop resistance to many drugs, it's essential that treatment ALWAYS include multiple drugs. Similarly, when a patient is failing treatment, you should NEVER add a single drug to the regimen. When you begin your evaluation of a failing regimen, you can't know which, if any, of the current drugs are effective. Adding a single new drug in a case where the resistance to the current drugs has developed would, in essence, be treating with only that one drug. Thus you risk losing efficacy of the new drug as well.

Another principle of TB treatment is that the duration of therapy depends upon the clinical response, the extent of disease, and the drugs used. Treating TB is not a cookbook. The four drugs shown here are the mainstay of TB treatment. For the purposes of this talk, I will use these abbreviations for Isoniazid, Rifampin, Pyrazinamide, and Ethambutol. Finally, directly observed therapy – or DOT – is an essential tool for ensuring completion of therapy. We'll come back to this point several times.

[SLIDE 5] ABOUT THE DRUGS: ISONIAZID

Let's talk a little bit about each of these four drugs. It's really important to understand the role that each drug plays in the treatment regimen as each does something slightly different. If you understand the role of each drug, it isn't necessary to memorize the drug regimens – they actually make sense. Each of the drugs varies in its capacity to kill bacteria (its “bactericidal activity”), to sterilize lesions (its “sterilizing activity”), and to prevent the development of drug resistance.

Isoniazid is the foundation of TB treatment. It's very good at killing organisms that are actively dividing, as we see at the beginning of treatment of a patient with active TB. This is when most of the organisms are growing, meaning they are actively dividing. INH, however, also has documented efficacy in the latent stage and has long been the first choice for treatment of latent TB infection. It is both effective and inexpensive.

[SLIDE 6] ABOUT THE DRUGS: RIFAMPIN

Rifampin is an effective bactericidal drug with a potent sterilizing effect, and is excellent at killing actively dividing organisms. Indeed, RIF is good at killing both active and quiescent (or dormant) organisms. Its sterilizing capability is so important that the use of Rifampin is necessary to shorten the duration of therapy to less than 12 months for active TB. So this is a drug you really need to understand. Knowing that discontinuing rifampin commits a patient to a much longer course of therapy will allow you to intervene if you encounter a clinician who is attributing a patient's gastrointestinal distress to RIF. You will want to ensure that the clinician understands the unique role of RIF and the ramifications of stopping this drug with respect to the duration of therapy.

In recent years, Rifampin has become increasingly important for treating latent TB infection and is now the standard alternative when INH can't be used.

[SLIDE 7] ABOUT THE DRUGS: PYRAZINAMIDE

Pyrazinamide is an often misunderstood drug. Although bactericidal, it is used almost exclusively for its potent sterilizing capacity. The important thing to know about PZA is that while it is very good at killing actively dividing organisms, it is much less good at killing quiescent organisms. This is one of the reasons we don't use it unless we have to for treating latent TB infection – a condition in which most organisms are quiescent. PZA is also very good at killing organisms in an acidic environment. This is important for killing bacteria inside macrophages and in situations where there's a lot of necrotic tissue. After the first couple of months of treatment, however, as most of the actively dividing organisms are killed, PZA becomes less and less effective. PZA's importance in rapidly decreasing the initial organism load is reflected in the fact that, to be reliably effective, treatment regimens that don't include PZA for the first two months must be extended to a total duration of at least nine months.

Let me say a word here about how we talk about appropriate duration of therapy to cure TB. Recommendations for the duration of therapy are based on population data. We cannot predict whether any given patient will be cured or will relapse with a particular regimen. What we can say is that, reactivation rates are unacceptably high in populations of people treated without PZA when the treatment duration is less than nine months. Similarly, reactivation rates are unacceptably high in patients treated without rifampin when the duration of treatment is less than 12 months.

[SLIDE 8] ABOUT THE DRUGS: ETHAMBUTOL

Ethambutol is an extremely important drug that may not be used when it should be used. Unlike the other three drugs, EMB is bacteriostatic rather than bacteriocidal at doses we generally use to treat TB. Nevertheless, EMB plays a key role. It is very good at preventing the development of resistance to other TB drugs. In a patient where drug susceptibilities are not yet known, the presence of EMB is crucial to ensuring that resistance to the other drugs doesn't develop if unrecognized drug resistance is present.

Pyrazinamide, on the other hand, does not prevent the emergence of resistance. So, for example, a patient who has TB with unrecognized INH resistance would be at high risk of developing rifampin resistance – and therefore multi-drug resistant TB - if the treatment regimen included only INH, RIF and PZA. The PZA alone would not be enough to keep resistance to RIF from developing. INH-resistant TB has become common in many parts of the U.S.

This is why we stress the inclusion of Ethambutol.

[SLIDE 9] THE BASIC REGIMEN

I've already alluded to the fact that drug resistance rates, particularly resistance to INH, are increasing. In California there are areas where INH resistance is as high as 33%. Therefore, it is increasingly important that treatment be initiated with all four drugs, unless you've got the susceptibilities already in hand before you start treating. Four-drug therapy is the "basic regimen" for initial treatment of active TB disease in the U.S. Directly Observed Therapy really should be considered for all patients. That said, while DOT for all TB patients is the gold standard, lack of resources can make this difficult. However, certain high-risk groups, including those with drug-resistant TB, should always be on DOT.

[SLIDE 10] INITIAL PHASE: FIRST 2 MONTHS

Recognizing that there are numerous exceptions, the standard, initial TB regimen for adults is shown here. The same four drugs are used for pediatric cases, but at different doses. The term “initial or induction phase” is used to refer to the first two months of therapy which is when the majority of TB bacteria are killed.

The standard initial regimen includes Isoniazid, 300 milligrams a day, and Rifampin 600 milligrams a day. For patients weighing less than 50 kilos, rifampin can be decreased to 450 milligrams. Pyrazinamide is usually dosed at the high end of its dose range at approximately 25 milligrams per kilogram to maximize its sterilizing ability, while Ethambutol is dosed at the lower end of the range, at approximately 15 milligrams per kilogram. The protective effect of EMB against emergence of resistance is as good at the lower dose as at the higher, and that’s the primary indication for EMB in the basic regimen. Exact dosing of EMB and PZA isn’t necessary as long as they stay within the dose range of 15-25 mg/kg. This allows adjusting the total milligrams to avoid, in most cases, the need for the patient to cut up pills.

[SLIDE 11] INITIAL PHASE: FIRST 2 MONTHS (2)

All drugs should be taken once a day. Doses should not be divided except in unusual circumstances. Not only is single daily dosing easier to comply with for the patient, there is good data to suggest that drug efficacy is improved with the higher peak serum drug levels that are achieved with single daily dosing .

As a rule, any patient not on DOT should get fixed dose combination therapy. There are two choices in the U.S, one of which is particularly convenient. 2 capsules of Rifamate combine INH and Rifampin at the usual doses, 300 and 600 mg respectively. For a patient who weighs more than 50 kg, rifamate is a good choice: two pills a day instead of three, one co-pay instead of two for insured patients. Patients like taking one less pill a day and they like paying less. From the public health perspective, rifamate is preferred because the patient always receives both drugs eliminating the risk of accidental mono-therapy if the patient forgets one or the other drug. For the Public Health case manager who is doing monthly pill counts, it's easier to count one prescription than to count two.

There is another drug, Rifater, which includes INH, RIF and Pyrazinamide. While useful in some settings, it can be difficult to adjust doses with this drug.

While there are initial phase regimens other than daily dosing included in the national guidelines, many of my colleagues and I feel that daily dosing is much preferred for its well studied and reliable efficacy.

[SLIDE 12] Continuation Phase: Last 4 Months

As we've just seen, the first two months is referred to as the "initial phase." The following four months of therapy for a standard TB patient is referred to as the "continuation or sterilization phase."

The continued presence of drugs clears the body of residual bacteria and helps prevent recurrence or reactivation. Before discontinuing any drugs, it is essential to know the drug susceptibilities. In patients where the drug susceptibilities are not known, four or at least three drugs, including ethambutol, are indicated for the entire treatment period. If the organism is fully susceptible, you have several choices for the continuation phase. The most common are those shown here: INH plus rifampin daily or INH 900 milligrams with Rifampin 600 milligrams twice a week. There are other choices -- for example, three times a week therapy. I prefer twice-a-week therapy because it is both less expensive from the perspective of personnel time for DOT, and less intrusive into the patient's life. This regimen is generally well tolerated. I do, however, take extra care to monitor the elderly and people with risk factors for liver toxicity.

DOT is absolutely essential for anyone on intermittent therapy. It is difficult to remember to take medication on only two days, and in a twice-a-week regimen, one missed dose is the equivalent of 4 days missed on daily therapy.

There is also a newer continuation phase regimen that includes once-a-week rifapentine, a long-acting rifamycin, plus high-dose isoniazid. This may be a particularly useful regimen for patients with access issues or in congregate settings such as jails or prisons where you can ensure the patient shows up for weekly therapy.

[SLIDE 13] ALTERNATIVE REGIMENS

There are some important situations in which the six-month regimen is not considered sufficient. The most common is patients who have cavitation on the initial chest X-ray and whose culture conversion to negative is delayed. These are people whose sputum cultures – cultures, not smears – are positive for longer than two months. The rates of reactivation in this situation with only six months of treatment are unacceptably high. Treatment must, therefore, be extended to at least nine months, even with PZA in the regimen. This is the key, but rarely recognized reason we always try to document sputum culture conversion to negative. The treating clinician should do sputum cultures monthly from initiation of therapy until cultures are consistently negative, as that time to culture conversion will let the clinician know how long to treat the patient. Remember, we also need to treat for 9 months anytime PZA is not included in the initial regimen.

[SLIDE 14] ALTERNATIVE REGIMENS (2)

For central nervous system TB, national recommendations are for 9 to 12 months of therapy. Many of us prefer twelve months for several reasons. One, the potential outcome for the patient if they reactivate can be serious or even fatal. Two, you don't have objective evidence of bacteriologic cure because there is no ability to document culture conversion as we do with sputum. Given this, some clinicians do not feel comfortable with the shorter duration of therapy.

[SLIDE 15] ALTERNATIVE REGIMENS (3)

Just a word on HIV infection. In most cases, six months of therapy for TB is adequate, but this is a setting where clinicians should have a low threshold to treat longer. Also, because of the documented risk of development of drug resistance, intermittent therapy is not generally recommended. There is an accepted intermittent regimen with dosing three times a week as long as all doses are done by DOT, but twice-a-week therapy is not recommended. In the setting of a patient whose status is somewhat unstable, daily therapy, particularly for patients on anti-retrovirals, has the advantage of increasing chances that you will pick up adverse events promptly because you see the patient every day.

Once-weekly rifapentine regimens are not only NOT recommended, they're contraindicated in HIV-infected persons. Rifapentine, remember, is a rifamycin, so it's in the same class as Rifampin. It is given once a week with high-dose INH. Studies with this regimen in HIV-infected patients show high rates of breakthrough with Rifampin-resistant tuberculosis. This likely represents the decreasing serum levels of INH during the week while Rifapentine levels stay high. So the organisms are essentially seeing a single drug for part of each week.

[SLIDE 16] REGIMEN 1

We don't have time to cover each of the recommended regimens in detail, but it's important to be familiar with the layout of the national treatment guidelines. As I have so far in this presentation, we frequently discuss appropriate duration of therapy in terms of number of "months." Assessing the adequacy of a treatment regimen, however, particularly if there have been breaks in treatment, is more appropriately done by reviewing the number of doses over an interval of time as is shown here.

The initial phase of therapy is listed on the left and the continuation phase on the right with the total minimum duration to the far right. The first regimen listed is the standard regimen we've been discussing: INH, Rifampin, Pyrazinamide, Ethambutol, seven days a week for 8 weeks in the initial phase, which is 56 doses. You then have three choices for the continuation phase. You can continue seven days a week, change to biweekly therapy, or switch to once-weekly INH with rifapentine.

[SLIDE 17] REGIMEN 2

This is the second regimen, what used to be called the “Denver Regimen.” This regimen differs primarily in that it is seven days a week only for the first two weeks and then changes to intermittent dosing for the duration of therapy. Patients on this regimen need careful monitoring for appropriate clinical response early in therapy and documentation of prompt, sustained culture conversion. We have seen cases of treatment failure with this regimen, particularly in patients presenting with extensive disease.

[SLIDE 18] REGIMEN 3-4

The third regimen is three days a week from the beginning. I've rarely seen this regimen used. The same caveats about patients with extensive disease would apply here. The fourth regimen is for people who can't take Pyrazinamide which would include pregnant women (in the U.S.), and persons with a history of clinical gout or sensitivity to PZA. You'll note that the total duration of therapy in this case is 36 weeks rather than 26 weeks, or 9 months rather than 6 months.

Because drugs used, clinical response, and compliance with the regimen can all affect the ultimate duration of TB treatment, it is important to avoid creating possibly false expectations by promising patients that their therapy will be only 6 months.

[SLIDE 19] TREATMENT OF DRUG-RESISTANT DISEASE

We don't have time to cover the treatment of drug-resistant disease in any depth. The primary principle is that treatment must be individualized to the patient and to the organism's susceptibilities. The most common patterns of drug resistance are INH resistance alone or INH plus Streptomycin resistance, a very common pattern in persons from Southeast Asia. In this setting, it is acceptable to treat with Rifampin, PZA and Ethambutol for the entire duration of therapy; all three drugs, all six months – assuming prompt culture conversion. Depending on the severity of the disease, an injectable agent or a fluoroquinolone can be added. The injectable is probably not necessary for the routine patient, who is not too sick, and for whom we anticipate good results.

[SLIDE 20] EXTRAPULMONARY TUBERCULOSIS

Extrapulmonary TB, particularly tuberculosis lymphadenitis, can be unexpectedly difficult to treat. Reciprocal growth – the development of new nodes while on treatment – is not uncommon. Deciding whether a new node represents a failure of therapy or just a hypertrophic node can be difficult. These patients must be managed case by case. What is always necessary, however, is to make sure the diagnosis is made in the beginning, including, whenever possible, submitting tissue for pathology and culture. This may require an excisional biopsy rather than just a fine needle aspirate. The more tissue submitted for culture, the more likely the organism will grow. That's key, because these patients are going to end up on six months of four drugs if you don't grow the organism and determine the drug susceptibilities. In fact, patients may end up on nine months of treatment even with documentation of drug susceptibilities. This is because a fair amount of lymphadenitis is caused by *Mycobacterium bovis*. And *Mycobacterium bovis* is inherently resistant to PZA, meaning we can't treat for only six months without risking relapse.

There has been considerable controversy about the use of corticosteroids. The current recommendations state that steroids are absolutely indicated in pericardial tuberculosis. There's clear data that steroid use decreases the risk of long-term sequelae such as pericardial constriction of the heart. Steroids are also strongly recommended for central nervous system TB, particularly if the patient has significant symptoms.

[SLIDE 21] ADVERSE REACTIONS: MOST COMMON

The most common adverse reaction that we see in our practice is rash. The key to dealing with a drug rash is remembering that any of these drugs can cause it. While it is very rare to see rash with Ethambutol, it does occur.

GI intolerance can also happen with any of the drugs. The simple fact of taking so many drugs on an empty stomach can also cause GI upset.

Liver toxicity can be caused by INH, RIF or PZA. Peripheral neuropathy is caused by INH but is relatively rare, and is even rarer when Pyridoxine is added to the regimen. The exact dose of pyridoxine necessary to prevent neuropathy is not known, but 10 or 25 mg per day are the most common doses used for adults. With optic neuritis we usually think of Ethambutol, but you should also know that INH has been documented to, quite rarely, cause this. Gout can occur with PZA, but usually only in patients with a history of clinical gout.

[SLIDE 22] ADVERSE REACTIONS: RASH

If a “rash” is not really a rash but only itching, you must first rule out hepatitis which can present early as pruritis. Once hepatitis is ruled out, an empiric trial of pre-medication with antihistamines is warranted. Pre-medicating the patient 20 minutes or so before the TB meds with a little Benadryl is remarkably effective but can cause sleepiness. Hydroxyzine (or Atarax) is a good choice with less somnolence. A petechial rash is very concerning. It doesn’t happen often, but suggests thrombocytopenia, a rare, serious, side effect of Rifampin. You must assume Rifampin hypersensitivity in this case. At that point Rifampin, and probably all rifamycins, should not be used again in this patient.

[SLIDE 23] ADVERSE REACTIONS: RASH (2)

It is rarely necessary to send a patient with a generalized rash to a dermatologist unless you're seeing a rash which is clearly atypical and likely not due to the medications. For the standard drug rash - usually generalized – red, bumpy, itchy - all the medications should be stopped. With most TB patients the drugs can be safely held for a period of time without starting additional medications. If, however, the patient is critically ill, it may be necessary to start an alternative TB treatment regimen. In this case, it is important to start at least three drugs to which the patient has not been exposed, so it will be necessary to use second-line agents.

After stopping the medications and when the rash has shown significant improvement, then a re-challenge can be initiated. The key to re-challenge is to not spread it over too long a period of time. It is not necessary to start one drug and wait two or three weeks before starting another drug. That is effectively mono-therapy and puts the patient at risk for the development of drug resistance. A new drug can be started every two days. These are hypersensitivity reactions and, if they're going to happen, they will generally do so within 48 hours. In our practice we usually start the re-challenge first with INH. I will often start with INH and Ethambutol, because Ethambutol so rarely causes rash. If the rash doesn't recur within two days, I will add RIF, and then if the rash still doesn't recur, I will add PZA. If the rash recurs, it is usually the last drug that was added.

[SLIDE 24] ADVERSE REACTIONS: GI

There are many things that can cause GI intolerance. It often starts at the very beginning of therapy. We are giving people, often people who never routinely take medications, a large number of pills to take every day and asking them to take them on an empty stomach. It's no wonder many people feel nauseous. I tell my patients, "Your body's getting used to having all these foreign chemicals in it, and that takes a little while."

Obviously, hepatitis must be ruled out. If a patient is presenting with nausea, anorexia or abdominal pain, stop all the drugs and check liver function tests. If the tests are normal, then it's not hepatitis, and you can proceed with trying to figure out how to get the patient through the GI distress. Pre-medication with anti-nausea medication can be useful. We have patients who have gone through 12 months of therapy with a dose of Compazine 20 minutes before each dose of TB meds and have done just fine.

Another approach is administering the medications with food. We will tell people to take the medication with a little bit of food, not a full meal and not fatty foods because that may decrease the bioavailability, especially of Rifampin, but a little food is OK, such as crackers, or a little sandwich or some rice.

[SLIDE 25] ADVERSE REACTIONS: HEPATITIS

Hepatitis is more problematic. Asymptomatic elevation of liver enzymes occur frequently but do not necessarily require discontinuing therapy. This is one of the reasons monthly liver function test monitoring of asymptomatic, low-risk patients is no longer recommended. Clinically significant hepatitis is defined as AST or ALT three or more times higher than the upper limit of normal in patients with symptoms or five or more times higher in asymptomatic patients.

Remember that all three of these drugs can cause liver toxicity. While there are many exceptions, INH-induced hepatitis is more frequently age-related. PZA liver toxicity, on the other hand, can be dose-related, but it is not generally recommended to decrease the dose in response to hepatitis. It is safer to discontinue the PZA even though the patient will likely need therapy for longer. Rifampin-associated hepatitis appears to be more idiosyncratic.

[SLIDE 26] ADVERSE REACTIONS: HEPATITIS (2)

Let's look at the management of drug-induced hepatitis. A transient rise in LFTs which then return to normal frequently occurs with the initiation of multi-drug TB therapy. For this reason, in asymptomatic patients, medications can be continued as long as the LFTs are less than five times the upper limit of normal. These patients require careful monitoring, however. For patients with symptoms, drugs should be held if LFTs are three or more times higher than the upper limit of normal.

[SLIDE 27] ADVERSE REACTIONS: HEPATITIS (3)

For patients with clinically significant hepatitis, careful evaluation and rechallenge is necessary.

It may be useful to consult with someone with expertise in managing these challenging patients. The first step is to stop all TB medications, as well as other potentially hepatotoxic drugs. While a complete drug holiday is best, critically ill patients who can't be off anti-TB therapy can be started on a liver-sparing regimen to tide them over. The initial evaluation should obviously include tests for other causes of hepatitis.

There are many ways to rechallenge, but always keep in mind that patients should not be left without protection from the emergence of drug resistance longer than necessary. A basic rechallenge can be accomplished by adding one drug at a time at weekly intervals. If the LFTs begin to rise after a week on the latest drug, that's an indication that that drug may be the cause.

[SLIDE 28] MONITORING THERAPY

Monitoring patients on TB treatment is important both to watch for potential side effects and to determine response to therapy. The baseline medical evaluation, symptom review, and laboratory tests listed here are standard. BUN and creatinine are needed to determine whether dose adjustment for renal insufficiency is required; CBC and electrolytes should be checked to ensure that they are normal at initiation of therapy; LFTs provide baselines against which to compare future workups; and uric acid, because of PZA and its association with gout.

Monthly face-to-face evaluation of the patient, including symptom review, is essential. This evaluation will guide you in determining whether other testing is indicated.

[SLIDE 29] MONITORING THERAPY (2)

Both sputum smear and sputum culture must be monitored but for different reasons. Documenting conversion of sputum smears to negative allows public health to remove restrictions, such as home isolation, that are put in place to prevent the patient with contagious TB from infecting others. The frequency with which new smears are ordered on a smear positive patient will depend on that patient's specific situation. For example, it is important not to delay documentation of smear negativity in a patient who is being restricted from working and is the sole provider for the family.

It is equally important to document culture conversion. As I mentioned earlier, it is necessary to know whether culture conversion to negative was prompt or delayed when determining the total duration of therapy. Generally, sputum cultures should be ordered monthly until they are consistently negative for a minimum of 2 consecutive months.

[SLIDE 30] MONITORING THERAPY (3)

A baseline chest x-ray is necessary for all TB patients, even if the patient has presented with extra-pulmonary TB. Remember that while the lung is the most common site of disease, TB is a systemic disease. It is the job of public health to ensure that a patient does not have contagious TB.

In monitoring pulmonary TB, monthly chest X-rays are not necessary. Changes on the radiographs just don't occur that quickly. The patient's clinical and culture status are better indicators of response in the short term. During therapy if the patient is progressing as expected, repeat films every three to six months are fine.

The CXR at the end of therapy is both crucial and frequently forgotten. Without a CXR at the end of therapy, post-treatment films taken later and compared to those early in treatment may miss subtle worsening of findings that could occur during reactivation or recurrence. The end-of-treatment CXR provides a new baseline for all future comparison.

Other recommended monitoring includes visual acuity and, if possible, color discrimination, if the patient is on EMB.

[SLIDE 31] POST-TREATMENT MONITORING

Monitoring after completion of treatment varies, but at least one assessment should be considered at 6 months after completion of therapy for patients with no drug resistance who had prompt clinical and bacteriologic response. Patients who had severe disease or poor response to therapy deserve closer follow up. Multi-drug resistant TB is an entirely different situation. Recurrence is much more likely and can occur a long time after completion of treatment. We follow our MDR patients indefinitely.

[SLIDE 32] CONCLUSION

This is Dr. Karen Smith, and in this session we've covered the essential principles of TB care. We've talked about the four drugs that are the mainstay of TB treatment, the adverse reactions associated with them, and touched on the monitoring of patients throughout therapy. Keeping these principles in mind will help you ensure that your patients successfully complete their TB treatment.

Thank you for your time and interest, and don't forget to review the supplemental materials.