

Grand Rounds Maximizing Rifamycins

January 2016

I want to first welcome everybody to Grand Rounds, and I hope you're all doing well. I know last week we had some challenges with the weather, and it really created quite a mess throughout the East Coast and beyond. And I hope everybody is staying warm and doing well. We're just so happy to have you. This is the first of our Grand Rounds this year, and I think this is going to be exciting.

I kind of think, to be honest with you, all of us have been involved in Grand Rounds and lectures and discussions recently about new drugs. And there has been a lot of talk about new drugs, new regimens. The Gates Foundation is trying to come up with a new regimen using totally new drugs. So now maybe once and for all, we can get a regimen that's more effective, less toxic, be quicker to use, easier to take, less side effects. Boy, doesn't that sound good, right?

But the bottom line comes down to right now, despite some new drugs, we really still don't have the promises yet that have been fulfilled for a regimen that's more effective or better proven or has better efficacy. And we're really at this point still where we were before. But we really maybe should appreciate a little better what we have.

As you know, we've had a very effective regimen for the last 50 or 60 years that has really proven itself as a major tool and weapon in the fight against tuberculosis, with potentially 80% to 90% efficacy and somewhat tolerable side effects. Although any side effect is not really tolerable.

The bottom line is the erythromycins really, really were a game changer. They were developed 60 years ago, came on the market, and took a disease that was once the most deadly and a disease without any kind of effective treatment and really gave us tools and drugs that gave us a shot at cure. And as you guys know, for the last 50 years, we've had those very good regimens. But it has its problems; and obviously, the big issue is that we may be losing it due to drug resistance. But luckily, for the vast majority of patients, the erythromycins work.

The question comes down to: Are we really using the erythromycins as effectively as we can. And as you know, there has been some new research that really suggests that maybe we should be using these erythromycins in a different way, maximizing them.

If you look at the physicians' death reference manual and you open it up, what you'll see is that there are all these warnings about using more than 600 milligrams of rifampin – that the skies will open, the clouds will turn dark and all horrible things will happen. But interestingly enough, we have been using the same dose for people for the last 60 years. But new research is now suggesting that maybe we could be using a higher dose. Maybe with that higher dose, we may get more effective use of the drug and, most excitingly, we may be able to shorten our regimen. And that's why we're lucky today.

We're lucky to have Chuck. I like to call him Chuck, and I know you've heard me introduce Chuck before. But to me, we've been very lucky in the TB field. Recently, there has been some research that if your name is Mary or John, you're more likely to be a genius. But in the TB field, we've been very blessed with Chuck. But to me, in my heart, there's only one Chuck, *the* Chuck; and that's Chuck Peloquin.

You guys know Chuck. Chuck is a professor and a Director with the College of Pharmacy and Emerging Pathogens with the University of Florida. Probably everybody on this call has had the opportunity to work with Chuck or has been interacting with Chuck. And as you know, where it comes to pharmacokinetic issues or pharmacological issues, Chuck is who we turn to turn.

And Chuck Peloquin is going to today talk about maximizing rifamycins and some of the issues and some of the potential limitations. And you know that when Chuck is about to speak, it's going to be entertaining; and it's definitely going to be memorable.

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So with that, Chuck, it kills me to say these nice things about you; but sometimes I have to. So, Chuck, how are you doing? What's going on?

Well, thank you, David, for that elaborate introduction. I was going to go by Sting, but that name was already taken; so I'm just going to go by Chuck. And today we are, as mentioned, going to be talking about the rifamycins and what we already know about them and what we can go and use them going forward.

So without further ado, and according to the WHO, TB is now No. 1. We're the single most lethal infection on the planet, and that's still includes the fact that if you're HIV coinfecting and you die, that counts as an HIV death and not as a tuberculosis death. So as you know, roughly 9 million people had active TB last year; and roughly 1.5 million people died from that. That comes out to one, roughly, every 20 seconds or 3 per minute.

So if I were to talk for about an hour – and I'll go a little bit past that – roughly 180 people will have died by the end of this presentation, and maybe you knew somebody. And this certainly seems to qualify as a serious problem from my standpoint, and I think you would agree with that. And so we have to look for better solutions beyond what we're already doing to try to bring these numbers down more quickly.

So what are we looking for? We're looking for highly effective regimens that are shorter than six months. And most people accept the fact that the regimen is six months, and I'll show some data that in many cases it goes past six months. But if we accept for the moment that it's a six-month regimen, what people are trying to find through experimentation are regimens that are shorter than that. Have we found it? Well, not yet.

And as you know, there have been three quinolone-based trials that failed to provide sufficient efficacy that failed to replace the current six-month regimen. That's not to say they didn't work; they just didn't work better, and they didn't work at a rate that would allow those regimens to be only six months long. So this is a very nice paper by Drs. Lanoix, Chaisson and Nuermberger at Johns Hopkins University. I encourage you to check this out in *Clinical Infectious Diseases*.

And they go through these three trials – the South Indian trial published in PLoS One in 2013 and then the two papers in the *New England Journal*, the ReMox study and the OFLOTUB study. So there were some encouraging signs in those papers, but it didn't qualify as a game-changing four-month regimen.

So why not? And the authors go into this in some detail; and, again, I encourage you to read their paper. Despite the inconsistent and altogether modest benefits of the fluoroquinolones in Phase 2 trials, large Phase 3 trials were organized and launched even before all of the Phase 2 results were available. So there was a little bit of haste involved, and there may have been reasons for that. But nevertheless, it turns out that they might have been a little bit too hasty.

And they also go on to say that future Phase 2 trials really should enrich for the patients who have the worst form of the disease, the cavitary form of the disease. So if you're trying to come up with a one-size-fits-all regimen, you really need to test it in the worst case scenarios, the ones with the worst cavitation, such that you can prove across a broad array, including the worst patients, that such a regimen would be effective. The non-cavitary, or minimal disease patients, still have to be treated; but if the regimen is effective for the worst cases, it should be better for the less severe cases.

So this begs the question should there be a one-size-fits-all regimen? And the answer for me is, no. Now, it would be really convenient; and people like convenient. I like toast in the morning, and the fact that the bread is already sliced for me is really convenient. So that's a situation where convenience is great. But maybe in the treatment of diseases we can't oversimplify and have one thing be the right thing for every single patient who comes into the clinic.

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TB, as you know, is a spectrum of clinical conditions ranging from the mild to the very severe, where you already have destruction of lung tissue. And for most other diseases – whether it's cancer or diabetes or hypertension or strokes – we stage those people; and we adjust the therapy and the aggressiveness of the therapy based on how we stage those diseases. And we generally don't do that with TB. Now, back to why not.

The quinolones do not appear to have sufficient sterilizing capacity. And as you know, there are sort of two flavors of drugs in TB – those that are able to kill the bacilli, but not necessarily all the forms of it that might be in your body. So you can have a drug, like Isoniazid, with great early bactericidal activity; but it may not be a great sterilizing drug. And sterilizing drugs are the most important because those are the drugs that at the end of the treatment, those are the ones that are going to prevent the post-treatment relapses in the patients.

And right now, we have two drugs that can do that based on the ways that we can measure it. And those would be Pyrazinamide and the class of Rifamycins; and the Rifamycins include rifampin, rifapentine and rifabutin. And we'll speak in detail about these three drugs. We're not going to speak in detail about Pyrazinamide today.

So why do we not have a magic four-month regimen? Drs. Lanoix, Chaisson and Nuermberger go on to speak about this in further detail. And what they say is that there are factors that contribute to the relapse diathesis, and these are multifactorial. They include higher bacterial burdens in patients with large cavitory lesions, reduced drug penetration to the site of infection, and lack of adequate immune effector function at the cavitory surface.

They also say that low systemic exposures to key sterilizing drugs, the rifamycins and pyrazinamide, due to pharmacokinetic variability among populations reduces the rate of sputum sterilization. And we're going to look at that in animal models, and we're going to look at that in clinical trials.

So if we think about these factors, you cannot control higher bacterial burdens. If a patient comes in with a 3 centimeter cavitory lesion, you can't say, well, I'm sorry; this clinic only accepts 1 centimeter cavitory lesions. You can't be treated here. That's not how it works. You get what you get. Whoever comes in the door, however progressed they are, you have to treat them.

And there's really not much you can do about the lack of adequate immune effector function at the cavitory surface. You could feed the patient and give them vitamins. You can get them some amount of bedrest. If they don't have shelter, you can provide that. But you can't really stoke the immune function at the cavitory surface.

So what can you do? Well, you can address the reduced drug penetration that was discussed by our colleagues from Hopkins. You can control the concentrations, at least in the plasma; and those are the concentrations that drive the amount of drug that enters the cavitory or other lesions where the tuberculosis resides.

So why are these soldiers using tracer bullets? For those familiar with the Second World War, you'd recognize these as Sherman tanks. Those are American tanks. And you might have seen the movie, Fury, from which this picture is taken. And you can see these flashes coming off the machine guns on these tanks, and those are tracer bullets. And tracer bullets have been used for a long time. And they answer the simple question: Am I hitting the target, yes or no?

So there are lots of different situations where people use measures to see if they're actually doing what they think they're doing. And you actually can do that in tuberculosis although you don't use trace bullets, per se.

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So how do we treat TB currently? The vast majority of TB patients in the United States are treated exclusively with TB drugs. So once you've made the diagnosis and maybe addressed some social issues of the patient, the actual treatment is comprised of typically four drugs. So you have to get the drug part right. If you don't get the drug part right, you're really in a world of hurt because that's 100% of your treatment.

Also, the vast majority of TB patients in the U.S. are treated with the same doses of the same drugs, especially isoniazid and rifampin. Now, there are historical reasons why these doses were chosen; but we also have to look back at what those reasons were and see if those reasons still attain today. And certainly in the case of the rifamycins, I would argue – as well as others – that those reasons no longer apply to our current situation. And we'll talk in detail about that.

Now, when we use a standardized regimen, we are assuming that these doses are the right doses for every situation. In other words, you have *the* dose for *the* patient; and every single person who comes in subsequently is *the* patient, the average patient from the British Medical Research Council Trials. And we essentially rule out a priori that the next person coming in might be somewhat different than the person we just saw.

Now, if you think about how you manage virtually any other disease, you don't do that. If you're treating hypertension, would you treat every single person with 50 mg of atenolol daily? If you had a diabetic patient, would you treat one after the next only with 10 units of regular insulin with each meal? And would you say, I don't care if their glucose is 30 or 300; they're getting 10 units of regular insulin. Or would you treat every stroke patient with 5 mg of warfarin once daily. I don't care if they're bleeding out or stroking out, they're getting 5 mg. No, that would really be bad practice; and the French term for that is *mal pratique*.

So what do we really do? We treat these patients by monitoring and getting feedback in one form or another to see how we're doing with our treatment. In the case of blood pressure, we have a convenient measure. We have a blood pressure cuff. We can just put it on the person's arm. We can check the blood pressure, and we can gradually dial up the therapy until we get the blood pressure consistently where we want it.

Likewise, we can measure blood glucose multiple times per day to make sure that we're treating the patient appropriately with whatever regimen we select. And likewise, the stroke patients – you would never give everybody the same dose of warfarin. You're going to try to get that Goldilocks not too high, not too low, just right INR value to make sure that the patient has a high probability of protection from further stroke without a high risk of a leading diathesis.

Virtually every other disease is moving towards personalized or precision medicine. In sharp contrast, TB continues to use standardized regimens that were developed decades ago. And we often don't confirm the adequacy of our doses. So I would say that does not qualify as precision medicine. It might be convenient medicine, but it's not precise.

So in TB treatment, the mantra is that it's six months long, and it's over 95% effective. And there is some truth to that. If you look at the original British Medicine Treatment Council trials, then you can show that under the per protocol analyses that were done, that is true. So what is a per protocol analysis? Only the patients who have actually completed the protocol as designed are included in the data analysis. Now, there's nothing wrong with that; and it's very informative. But you exclude people who are otherwise going to be showing up in your clinic.

So if you look at the typical BMRC studies – and there are a lot of them published, and there was a complete review by Fox and Mitchison in 1999 in the so-called *Grange Journal* or the *International*

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Journal of TB and Lung Disease. So you can pull all of these, and many of them are referenced in the TB Guidelines as well. On average, there were about 10% of the patients who were evaluated but not assigned to the study and another 10%, approximately, dropped out of the study. And each one is a little bit different, but these are typical numbers.

So you lose about 20% of the patients who were evaluated, that never made it into your data analysis. So if you put them back in the pool, then you're really looking at 75% of the patients who were evaluated in these analyses. So when we talk about this six-month regimen, well, that was really as applied to 75% of the overall patients.

Now, if we look at completion rates in the United States – now, we don't track relapse in the United States directly. We have completion rates in the United States. And you can see that at the peak of the rebound or resurgence of TB, only about 64% of the patients were completing therapy. And by 2000, this had really gone up into the low 80%; and it went from maybe 82% to 84% to 85%. And now it's around 88%-89% of the patients who complete their therapy in one year or less. And the fine print here is a little hard to read, so I will click to the next slide.

And now it's not the so fine print; it's the big print. So this is continually updated at the CDC; and this last culling of the data is as of last June, and it includes patients who were alive at diagnosis, were treated with a regimen and didn't die during therapy. So that seems fair, and these are candidates for drug therapy; and they completed the drug therapy. And it excludes patients who had drug resistance or disseminated disease. In other words, these are patients who might otherwise be candidates for a six-month regimen.

Now, if we look at the data where I have more additional data from the CDC -- it's the 2010 slide set published in 2013, as you can see here but the data is up to 2010 – but it's really the same data; it looks the same. And when you say completed in one year or less, well, it begs the question: How much less? And so I asked the CDC if they could tell me, and they almost instantaneously did. They were very, very helpful; and they provided this table.

So if we look at six months only, or six months or less, only about one in five patients in the U.S. as of 2010 completed what could be the six-month regimen in six months. And you might argue, well, there are bureaucratic reasons for that. They have to go from, perhaps, a hospital to a public health service; and there's time for the bureaucracies to talk to one another and transfer patients. Fine, let's just look at seven months. Well, it's 45%; it's not 95%. And you would expect that at maximum it could be 88% because that's what the previous slide showed us it was. It was 88% at one year.

I would encourage the CDC to publish this slide right after the other slide that they always publish in annual slides because this is where we're going to get traction. If we start using alternative methods, or different regimens or higher doses, we're going to move these 80% and 90%, hopefully, numbers earlier and earlier in treatment. We may not get more than 95% cured, but we can cure them faster. And faster means it's less difficult and less expensive for the TB clinics. And it reduces the time that the patients are exposed to drugs, and it reduces the times that they can have adverse drug reactions.

So what? Well, it's supposed to be a six-month short-course regimen. And if it's taking you 12 months or longer, that's not short course anymore. And, again, you have to pay for each and every month. There are no BOGOs, buy one get one free. You can't just say, well, I'm going to pay for the first six months; and we'll just do the others for free. You have to pay for the drugs and the follow-up and the labs and the DOT for every month that the patient is under your care. So you have an incentive to get it over with.

Another thing is that if we look at those original BMRC studies that I was just talking about, we're really not giving the same doses anymore. And if we just look at rifampin, the average weight of those patients were predominantly male in the Hong Kong and East Africa trials. Their weight was only 48 kilograms. So

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if we take 600 and divide it by 48, that's 12.5 milligrams per kilogram, which is above the sort of standard 10 milligrams per kilogram that we think about for rifampin.

But if we look at some of the large patients that we have today, 90 kilograms, while it seems large, is not outrageously large for a U.S. patient. Then, we're only giving 6.7 milligrams per kilogram; and that's quite a bit different.

So it's a really simple concept. If we consider the original study patients to be full of rifampin – and you could debate that – but if we just considered that the baseline, the gold standard – notice the gold here. If that's the gold standard, then we're really doing something quite different. These guys are full; these guys are not full because they're dramatically bigger than the patients who were studied.

Another way of looking at it – if you have a little Cooper MINI, you can fill it with 10 gallons of gas. But if you have one of these big Chevy Avalanches, you're not going to fill it with 10 gallons of gas. It may not even be half full. So it might be a very manly-looking vehicle, muscular wheel wells and all of this plastic on the deck – and what could be better than that – but nevertheless, this manly-looking truck is going to suck a lot of gasoline. And if our big patients are used as an analogy, then you're going to need a lot more drug to fill our big patients.

Let's get on to the pharmacokinetics and pharmacodynamics part of the discussion here. And some people are intimidated by these terms, but there's absolutely no reason to be intimidated by these terms. And I'm going to show you lots of pictures of what they mean.

Pharmacokinetics is simply what the body does to the drug. The drug goes in; it moves around to different places in the body, and then it goes out. So that's not really that complicated; it's just a long word. But if you like PK, then it's suddenly a short word.

And then pharmacodynamics, if we were using a drug like an antihypertensive drug, it's what the drug does to the body. In the case of antibiotics, we're going after a parasite of some type inside the body. So we're looking at the ability of a drug to produce an inhibitory or lethal effect against the organism inside of our patient, and hopefully not doing anything else to the patient.

Another important concept is the minimal inhibitory concentration or MIC. And in other disease states, you might see MEC, the minimum effective concentration. But this is really a critical idea. When you get your results back from the laboratory saying it's susceptible or resistant, they might not have done a full MIC testing; but they did sort of the shortcut version, the critical concentration or epidemiological breakpoint concentration.

And where do these concentrations come from? Well, it was based on achievable concentrations in humans. So if you go back to the agreements in the 1960s – and all of these are summarized in the book by Leonid Heifets from the CRC Press that was published in 1991 – you can read the long-play version of the history of susceptibility testing for TB. But it really comes down to a version of the minimal inhibitory concentration. And if you're below the minimal, you're not inhibiting; it's a real simple concept. You're either under the bar or you're over the bar – or you can actually run into the bar. But you have to take this into account, and it was all tied to achievable human concentrations.

So how do these drugs work? A drug is just a chemical; it's just a chemical that we happen to know something about, and it's going to do something desirable in the patient. And in the case of antibiotics, these antibiotics have to find the organism – and it's complete random chance – and then they have to bind to that target inside the organism, and that produces an inhibitory or a lethal effect. So unless the drug is delivered to where the bug is residing – in other words, unless you have adequate PK – nothing happens. You don't get pharmacodynamics or PD. So it either gets there or it doesn't.

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Here are the pictures that I previously mentioned were coming. And when you look at them, they're really not that hard to understand. Pharmacokinetics is concentrations over time. The drug goes in; it reaches the maximum; and then it is eliminated from the body. So that's pretty straightforward.

And then depending on whether we're looking at an in vitro system or an in vivo system or even looking at human data, there's some dose below which nothing happens. And then as the concentrations get higher and higher, something starts to happen. And then you reach concentrations beyond which no more benefit is gained. And then you put those together, and you get effect over time.

So these are really not that radically difficult concepts, and there's a lot published about this; so you can read more about it.

Specific to antibiotics, we're looking at the area under the curve or AUC. And this is really what's driving the bus. So here's our MEC or MIC, the minimal inhibitory or minimal effective concentration. And for some drugs, we have the maximally tolerated or minimally toxic concentration, whichever you prefer. And then if you stay below this sort of toxic range and above the minimally effective range, you're in the therapeutic range. And it's not quite so simple, but it's a good illustration of what's going on.

Not every TB drug has concentration-related toxicity, so we don't always have to worry about that. Rifampin seems to be largely devoid of that kind of toxicity whereas ethambutol, yes, if you give enough ethambutol, you can get into problems with ocular toxicity. So we have the peak concentration, or C_{max}, and we have this AUC. And those two relative to the MEC or MIC is really what we're trying to maximize in order to kill the maximum number of organs. 30:22

So the killing of TB by most drugs can be well-described by the AUC to MIC, so the area under the curve I just showed you divided by that MIC or MEC; and more is better. The higher the AUC, the more killing that you get. For drugs that display this kind of activity – and that would include INH, rifampin, PZA and ethambutol – those are considered concentration-dependent killers.

There's another class where having the drug maybe four times the MIC for a long time most of the dosing interval – such as beta-lactams like penicillin and cephalosporins – those are time-dependent drugs. But we're not going to be talking about time-dependent drugs today.

Now, all of this has been known for a long, long time. And the earliest studies with the TB drugs basically had this information if they didn't exactly call it by these terms. Again, what we want to do is maximize this AUC relative to the MEC or MIC. And really, this is the whole show right here. And you really need to understand this, and you're going to keep seeing this slide because it's really the key point about this. The bigger this AUC gets – if this gray area was all the way to the top of the slide relative to the same MEC, you're going to get more killing; and that's exactly what you want to get.

If you want to read more about it, there was this really nice paper in *Nature Medicine* last year, Brendan Prideaux, along with Laura Via, Cliff Barry and Veronique Dartois did a really, really nice job discussing the association between sterilizing activity and drug distribution into tuberculosis lesions. It's not just enough to get it into the plasma; the plasma is delivering it to the lesions themselves. Now, normally we can't measure the lesions in our patients; so we don't have access to that in most clinical circumstances. But in this study, they look at it under experimental circumstances.

Also, if you want to read more about optimizing the clinical pharmacology of the tuberculosis medications, my graduate students, now graduated, Eric Egelund and Abdulla Alsultan, and I wrote this paper also last October. This one is in *Clinical Pharmacology and Therapeutics*.

So this is you. You're so brave; you don't even wear a helmet. You've got the headphones on; you're barking out orders. Your mouth is open, kind of like Dave Ashkin; and bang, here's another dose being

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given to your patient. And here's another one; and down here, those are all the doses you've already given, all the shells you've fired. And what's this thingy here? Well, this thingy right here is how you aim.

Most weapon systems have an aiming device. That's why they have the old saying: Ready, aim, fire. And we can actually aim in tuberculosis as we treat patients, and that's something we'll talk about. So if you've aimed carefully and, bang, you just shot down this airplane. And it's not going to blow up your ship, and that's a good thing.

But what if you'd missed? What if you did not aim carefully? Oh, I hate it when that happens. So the old saying: Sometimes you get the bear; sometimes the bear gets you. And look at this guy; he's like, oh, shish kabob. So he's very unhappy down here. He's got his hands on his head because he knows that his ride home just got blown up.

So even though I'm always loathed to show target slides in pharmacokinetics because it takes people off the topics I'm trying to give to them, it's easy to explain things using this. So the top left, we have low precision and low accuracy – just all over the place. Here we have high precision; they're all clustered together, but they're not in the middle of the target where we want them. Here we have accuracy if the target is the yellow band out here; but in our case, we want it here – we want it in the middle. So we have low precision, high accuracy, but not on the target that we're shooting for. And this is what we really want; all of the shots clustered right where we want them. And in this case, it would be all of the drugs being delivered very effectively to the lesions where the TB are and rapidly killing those tuberculosis bacilli.

Now on to high doses of rifamycins and rifamycins in general. Here's our friend rifampin, the best drug ever and one of the primary drugs for TB. It really disrupts the DNA-dependent RNA polymerase. And if you don't have RNA functioning, you're not going to be making any proteins; and things are going to come to a screeching halt inside of that cell. Rifampin can be given orally or intravenously. The standardized dose is 600 milligrams daily.

And I've had a chance to talk with some of the originators of that dose, Denny Mitchison being one of them; and Denny said, "Well, you know, Charles, 600 milligrams rifampin is the minimally effective dose of rifampin." And if you look at the suggested readings for today's presentation, several of those papers discuss that in detail. So I won't belabor the point. There were good historical reasons for picking this dose, but those reasons no longer pertain here in 2016.

Rifampin is largely cleared by the liver, and it has a low amount of hepatotoxicity. If you give really big doses intermittently, like 1,800 milligrams once a week, then you have, after several months, a probability of flu-like syndrome. But if you give it daily, that doesn't happen.

Now, rifapentine is cyclopentyl rifampin. So they took rifampin and they put a lipophilic sidechain on it, and that causes rifapentine to stick to plasma proteins. And by doing so, the liver can't get at it; and it hangs around longer. So it has a longer half-life. But it's not necessarily the way we would want to get a longer half-life.

Everything else is mostly the same as rifampin. It's not available intravenously. Based on the studies which I will present today, we're moving from a 600 milligrams originally twice- or once-weekly dose and then 600 milligrams daily with Study 29 to 1,200 milligrams daily with Study 29X from the TB Trials Consortium. It's cleared through the liver, like rifampin, and has similar toxicities to rifampin because it's mostly rifampin. It's cyclopentyl rifampin.

And then there's rifabutin, which is given instead of rifampin for HIV-positive patients or other patients at high risk of drug/drug interactions. You may remember the old commercials: Stuffing instead of potatoes. So here we have rifabutin instead of rifampin. And it has the same mechanism of action; it's only available orally. The dose varies depending on the other drugs you're giving because there are two-way drug

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interactions with rifabutin. It's cleared by the liver, but the toxicities are different than rifampin or rifapentine. And, unlike rifampin and rifapentine, the toxicities are concentration-dependent.

If we compare these drugs, rifampin used to be the all-star for drug/drug interactions involving cytochrome P450 3A4. And in the original study is if you only give rifapentine twice a week or for a short period of time, it was a little bit less potent than rifampin. But if you give it at 1,200 milligrams daily, it's at least as potent an enzyme inducer as rifampin. So it's not going to help you in those situations where you have a lot of drug/drug interaction potential.

Rifapentine is 99% protein bound, and that's not necessarily a good thing. It doesn't have to be a horrible thing, but it's not necessarily a great thing. Rifabutin – a lot less drug/drug interaction potential but a different set of toxicities. So that's the quick comparison of the three.

If we look at their potency against the minimal inhibitory concentration – that number coming up again, THAT MIC, right – rifampin is either two to four times less potent than rifapentine or rifabutin in vitro, and here are the peak concentrations. Rifapentine actually is somewhat higher than that, but this makes the math easy and easy to compare.

So you'd say, well, rifapentine has got the best C_{max} or peak to MIC ratio; so that should be the best drug, right? Well, this is total drug; so it's including the amount that's bound to the albumin molecules. And the albumin molecules are really, really big; and they don't move inside of the TB organism. So rifapentine has to come off that in order to get into the bacilli. And so it can serve as a storage center, but it's not active drug because it can't drag the albumin in there with it. So if we take the bound drug out of the equation and only look at free drug, at least on the peak to MIC ratio, rifampin is actually better.

So the debate continues of which of these two drugs ultimately will be the preferred rifamycin, and you can make an argument for either one. We'll talk a little bit at that today, but it's not the primary focus of parsing out those two drugs.

Here is an old study. It was a late breaker once back in 1969, when I was 10 years old; but it's not a late breaker now, and it's been out for a long time. These studies were done in inbred mice. The nice thing about inbred mice is that you can get a whole group of them, and they're all six weeks old, say; and they're all about the same weight and they're all from the same family and they all are more or less the same pharmacokinetically, much more so than humans.

So you can use standardized doses; and, from mouse to mouse, you're going to get pretty much the same concentrations. So here's the dose we give, 10 milligrams per kilogram; but at least in this experiment, which was 10 weeks long, there's still plenty of viable bacilli that could be plated out and measured. And there are other forms that might be there that are very hard to measure on solid auger, so there actually could have been more bugs than this.

But if you went up to 40 milligrams per kilogram, and the intended concentrations with that, at least under the conditions of this experiment, there were no viable organisms left. Now, this is not a relapse study, which is really what you want to ultimately do. This is just a cidal study; nevertheless, it's very encouraging about the dose effect of rifampin.

So this is what we're talking about – as you make this AUC bigger and bigger and bigger relative to a standardized MEC or MIC, you get more killing – just like this row here. And you see the number of bacilli dropping off fairly dramatically. So if it were my lungs, at the end of the day, if I had no more toxicity from this dose relative to this dose, I'd certainly rather zero bacilli residing in my lungs than a whole pile of them residing in my lungs.

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So right from the get-go, there were a lot of questions about: What's the dose of rifampin? And I've already said that the 600 milligram dose is the minimally effective dose. The debate started in '72, and it really hasn't stopped.

Here is a study done by the British Thoracic Association, now the British Thoracic Society; and it's very much modeled after the BMRC studies, which were done outside of England. This was done inside of England. And we get pretty standardized results. This is what we expect; roughly 70% to 80% of patients will be culture negative at two months, and this is exactly what these guys show.

But let me draw your attention to a couple of things. Just like the BMRC studies, they gave a dose of pyrazinamide that was 35 milligrams per kilogram. For the smallest patients, those under 45 kilograms, those people got 1,500 milligrams. And then the bigger people got 2 grams of pyrazinamide daily. We don't usually do that in the United States. And they gave 25 milligrams per kilogram of rifampin, not 15 milligrams. So they were giving more aggressive doses. And we still say that we're going to get these results, but we don't give those kinds of doses to our patients.

Meanwhile, on the other side of the English Channel, Kreis and Pretet were looking at high doses. And they were giving 1,200 milligrams of rifampin and 900 of isoniazid, either daily or every other day, along with daily streptomycin. And they got these kinds of results. And notice they didn't use pyrazinamide, which certainly adds to your two-month culture negativity rate by about 13%.

If we just stand these studies side by side – this is not a statistical comparison – but it does kind of look like if you give bigger doses of the drugs, you shift your endpoint a month early. So you've killed off, in most patients, the largest number of TB, which is exactly what you want to do. So even this old study from '76 is very encouraging. They didn't have flu-like syndrome; and even with highly intermittent rifampin regimens, you usually don't see that until about three months into the regimen.

So here are two references that you can read more about -- one I'll come back to, and it's also on your suggested reference list – speaking about doses of rifampin.

Here are my consiglieri – my uncles in the business. And most of you know that this is Denny Mitchison; officially, he retired last October at age 96. This is Jacques Crosieux; he's 86, and he continues to do TB research at Johns Hopkins University. And this is my colleague from National Jewish, Leonid Heifets, who, sadly, passed away at age 89 last May; and I do miss him dearly. And this is near Colby College in New Hampshire. And I had a chance to talk with these guys about the history of the doses that we did. And I had excellent input from them and subsequently wrote this paper, which was previously mentioned, in 2003 about what is the right dose of rifampin.

Now, also at that 2001 meeting, a gentleman from AstraZeneca, from their Bangalore, India branch were there; and we had a nice discussion. And they went back and did these studies. And this is a six-day acute infection model of TB. And as you can see, AUC to MIC is a main driver for these drugs and, in this case, for rifampin. This is where we are on the curve with the standard dose, which is barely effective; and that's speaking to Denny's point about the minimal effective dose of rifampin. And you can see that even in six days, you can get nearly a four-log kill if you're willing to really crank the dose of rifampin. And four-log kill is 99.9% of the all the bacilli are dead within six days, so that's incredible.

Again, the bigger this AUC compared to the MEC or MIC, the more killing that you get. And it's not just true in animals; it's true in people. And we'll get to that.

Again, if you're giving a big enough dose, you're going to get a massive amount of kill of TB; and that's exactly what you want. These two slides – the last one and this one – are really saying the same thing; they're just showing the picture differently.

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Let's move from the lab to the clinic – enough about mice and let's talk about people. What happens if we go in the other direction? What if you reduce the exposure of a concentration-dependent TB drug? Well, that was not the intention of this study; but that was the outcome of this study, which is the TBTC Study 23. And this is the 23 A, which is the PK sub-study. This has been out for a decade, so this is not brand new. Nevertheless, it's highly illustrative of the point.

So this was the study of intermittent rifabutin-based regimens in HIV-positive TB patients. And the results were not subtle. Now initially, before we had completed the study and then after the study measured all the concentrations – we had the results of the study clinically, but we didn't have the concentrations yet – everyone focused on the CD4 count, and it seemed like the guys with the lowest CD4 count did the worst. But once you controlled for the area under the curve or the Cmax – both were highly correlated – for rifabutin, the CD4 count dropped out.

An odds ratio of 1.04 is essentially an odds ratio of 1, which is (inaudible). It doesn't matter what the CD4 count was. The driver was the rifabutin area under the curve. And 50% of the data are in the boxes. So 50% of the data is right here; and 50% of the data, or more, is right here. And you can see that these two are separated. So the guys who not only failed to relapse but had acquired rifamycin resistance had much lower exposure to rifabutin; and they were getting that intermittently, which is a double whammy because on the days off, you have zero AUC.

The moral of this story is that if you don't kill the pathogen, you select for drug resistance. And that's exactly what you'd expect from in vitro in animal model studies. And acquired rifamycin resistance was avoidable had these protocols had a built-in dose adjustment scheme based on concentration. That wasn't part of the protocol; we weren't expecting these results, obviously. So we didn't build that into the study. If we were to do the study over again, we probably would build that in.

But further, there's additional cases. Liz Jenny and Kareen Joseph had three cases of this, acquired rifamycin resistance. And then our group here in Florida, in a PK study where you're not supposed to have any clinical endpoint, had a failure with acquired rifamycin resistance. So overall, the AUC is a very big player with rifabutin. Rifabutin is the poster child for therapeutic drug monitoring because you really don't want to be too high because there is concentration-related toxicity. And you definitely don't want to be too low because you get acquired rifamycin resistance, which is really bad.

There are over 12 reported cases of acquired rifamycin resistance in the literature, and that doesn't speak to other cases that were never reported. But there are a dozen cases in the literature with low rifabutin exposures in HIV-positive patients. This is pharmacodynamics in action, but it's not the kind you want; we're going in the wrong direction here.

Interestingly, in conversations that I have as I speak with different clinicians, there is some reluctance among some centers to use rifabutin therapeutic drug monitoring for these kinds of cases, even though the acquired rifamycin resistance is completely avoidable. It is trivial to change the dose and move the concentrations up; it's very, very easy. Why? Well, people think it's too expensive.

So let's look at that; is it too expensive? According to Susan Marks and colleagues at the CDC and around the country, they came up with these estimated costs. The average, garden variety of TB in the United States costs around \$17,000. That's the average number; of course, there's a range around that number. MDR-TB, around \$133,000 and XDR around \$430,000, just on average. Here are the costs; if you only measured the rifamycin, it would be \$140 for 2 time points; with rifabutin, it's 3 points and 7 hours; for rifampin, it's 2 points and six hours. And there are multiple labs that can do this for you. And then if you measured all four, it would be around \$560, depending on what lab you went to.

Now, just one case of MDR-TB is going to set you back \$133,000. That's a lot of money. And you've already sunk the \$17,000 for the first treatment; so now you're into it for \$150,000, which is approximately

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1,000 times the cost of doing TDM. So for \$133,000, you could get 950 pairs of concentrations; or you could do all four drugs in 237 patients. Again, there are already a dozen reported cases, plus whatever cases were never reported. If we just look at the reported cases, we've already plunked down \$1.6 million to rectify the situation for those 12 patients. That equals 11,400 pairs of concentrations; in other words, a pair of concentrations for more than the total number of TB cases annually in the United States.

Based on that, I would have to say that TDM, especially with rifabutin but in general, is not too expensive when you consider the alternative costs. So as they say on those commercials: What's in your wallet?

Now let's take a look comparing TB to something that is done here at the University of Florida and lots of universities around the United States, heart/lung transplants or solid organ transplants in general. Here we have \$1.2 million for one patient. And now here, we have \$17,000 for one patient. But we're always trying to angle for: Can I only treat them three times a week? Can I treat them two times a week? Can I cut this number?

What is it about the heart/lung transplant patient that we're willing as a society to pay \$1.2 million for that one life; and, importantly, what is it about TB patients that we're not willing to pay that kind of money for these patients? And these get into some very difficult societal questions, which I'm not going to rehearse here today. I'll let you think about that. What's the difference between these patients and these patients? And why are these patients worthy of \$1.2 million and these aren't worthy of even \$17,000? That's a good question.

Do you think these guys here in this turret were thinking, well, yeah, we're about to be killed by these airplanes; but at least we didn't use up all our ammunition. I don't think they were thinking that at all. So I think we try a little too hard to skimp on the cost of TB treatment. And for other disease states in the United States, we don't even worry about the cost.

So let's get back to pharmacokinetics and pharmacodynamics. Why is acquired rifamycin resistance happening? It's happening because of this and the pharmacokinetics and the pharmacodynamics of these drugs that spell the story for us.

Let's look at rifamycin. In the blue line, we have to the total drug concentration; but some of that's bound to albumin, and it's not really helping us. It's the free drug concentration, which is only about 15%. It's 85% protein bound; therefore, 15% is free drug concentration. So this is the business end here; this is the stuff that can readily go out to the lesions and inside of the mycobacteria. So that's the picture of rifampin.

Let's look at rifabutin. And at a standard 300 milligram dose, we barely reach the MIC or don't even reach the MIC, at least in the plasma. It might be a little higher in the lesion, but it's not a lot higher in the lesion. Now, what if we doubled the dose? Well, we would get above the MIC but not a lot. And the other troubling thing is that we have this low concentration that hangs around for a long time. This is along with the 36-hour half-life, so it's going to be there for a long time. It's like those Snickers commercials: Not going anywhere? Get a Snickers.

Here's rifapentine – lots of drug, but it's all bound to albumin except for 1%. I'm going to blow this up so you can see it. Here is the free drug concentration, but the values here are really tiny. And it hangs around for a long time, and that's a mixed blessing. If we put the three together, you can see that rifapentine is in the red; rifabutin is kind of weak, and it's in the orange; and rifampin is in the blue in this example; and the MIC is the rifabutin/rifapentine MIC.

The other interesting thing is that this AUC, although it's vertical, is pretty similar to the rifapentine AUC, which is horizontal. Overall, they're kind of similar; and that's not too shocking; it's rifampin against cyclopentyl rifampin.

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Now, if we compare it to the companion drugs – and I'm not putting pyrazinamide on the screen because it's off-scale, plus it doesn't really protect the other drugs from resistance. It's doing its own special thing; it gets a special population. INH, rifampin and ethambutol are pretty evenly matched here. They're in the same range, and they're all pretty much gone by 24 hours. There's a tiny, tiny, tiny amount of ethambutol left; but, for the most part, they're gone.

Now, if we look at rifabutin, it's not well-matched. It's way below the other two; and, after 24 hours, the rifabutin is still there all by itself. So if you give an intermittent rifabutin regimen, it's there by itself every other day. Rifapentine is there by itself every other day – at a higher concentration, but it's still by itself after 24 hours. So rifampin, INH, PZA and ethambutol are reasonably well-matched pharmacokinetically. If you were able to give them all daily or all intermittently, they're all going to get in and get out at roughly the same time.

You can give the other two drugs daily, and you avoid this problem altogether. But if you give intermittent rifabutin, you will be stuck with sub-MIC rifabutin concentrations as monotherapy about three days every week; that's bad. And then with rifapentine, at least it's above the MIC; but it's monotherapy about three days a week. That's why I'm not a big fan of intermittent therapies, especially early in treatment when there's lots and lots of bacilli. I'm not a big fan overall, but especially early in treatment.

Coming back to that question that keeps coming up: What is the right dose of rifampin? Martin Boeree had a really nice poster at the CROI meeting in 2013; and, happily, some of this has been published. Let's get into that. There are two nice papers by Martin and his colleagues from the Netherlands, the first in the *Gray Journal* in 2011 and then in the *Blue Journal* in 2015. We have the blue and the gray; it's kind of a Civil War theme, I guess. Nevertheless, these are very good papers; and I encourage you to read them in detail.

What did they have to say? They did a series of three studies, which were underway at this time in 2011 and now are approaching completion. They did a PK study in TB patients, and they did dose escalation; and we'll talk about that in detail. And then they did a Phase II study. And our group, which includes Carol Mitnick at Harvard and Jerry Davies in Liverpool, England, are doing another study very much like it down in Peru. And then the third study that our colleagues from the Netherlands did was a Phase IIB study of the highest-tolerated dose in 200 patients across three countries. I think that is proceeding towards completion as we speak.

What did they find in the first study? That's the one that was published in 2015 in the blue journal. And they went up to 35 milligrams per kilogram. Now, remember the study by Ludo Verbist, the one from 1969? He went up to 40 milligrams per kilogram, so this is getting close. But in a 70-kilogram person, that's 2,800 milligrams, 2.8 grams – which might seem like a lot, but if this had been the originally studied doses of rifampin, we wouldn't blink at it. We don't worry about 2 grams of cephalosporins or 4 grams of piperacillin. We don't even worry about that because we say, oh, well those are well-tolerated. I think that you'll find that rifampin in big doses is well-tolerated also.

So they gave monotherapy just for 7 days, and then they added the companion drugs for days 7 to 14. And the adverse effects really were not dose-dependent, and they got more than proportional increases in the P concentration in AUC. As you give bigger and bigger doses of rifampin, you saturate some of the processes that spit it back out into the bile and into the gut; and you get a BOGO. You get a buy one, get one free. You get more than proportional concentrations as you escalate doses of rifampin.

The opposite happens with rifapentine; the bigger the dose, as a percentage, the lower the bioavailability of rifapentine. But you can escalate rifapentine doses also. So here there was high inter-individual variability. Knowing the dose didn't tell you what the concentrations were. Measuring the concentrations told you what the concentrations were. And the greatest reduction in the sputum colony counts was with the highest concentrations, which is exactly what all the mouse models and the in vitro models told us. It's

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exactly the story from rifabutin, except we're going up instead of down here; so this is going in the right direction.

And then the last paper I'm going to talk about is the study about what's called 29X or high dose daily rifapentine in this study in the blue journal by Susan Dorman and colleagues with the TBTC. This was a prospective randomized study of three doses of daily rifapentine. And unlike rifampin, which is better on an empty stomach, rifapentine is better with food. And they compared 10 milligrams, 15 milligrams and 20 milligrams per kilogram to the standard 10 milligrams per kilogram of rifapentine – I should have put "of rifapentine" in here. But anyway, they're comparing it to a standard TB regimen with rifapentine, and all the patients got these companion drugs.

There were 1,135 patients assessed, but only 334 patients actually made it through the study. So 70% of the people assessed were eliminated a priori. Now, think back to those BMRC studies, where I was saying about 10% were not included and 10% dropped out. Overall, you don't have 95% efficacy overall because you really only have about 75% to 80% of the patients to evaluate. So here, we have additional patients who were excluded from the study.

And then there are the three types of analyses: the per protocol, as done by the BMRC; the intent to treat, in other words, if you're randomized, you're in the analysis; and then the modify, where it's usually you have to have a certain minimum number of doses to be in the analysis. You can see the three different analyses here, and it looks like on this particular display some of the numbers shifted. The lower row, you have to picture it being under the other ones. So we have the rifampin and then the three rifapentine arms. And if you look at the number of patients who were in the per protocol relative to the intent to treat analysis, it's close to that 75% number that I mentioned from the BMRC study. So not everybody is able to be analyzed when they go into a clinical trial if you want to take everything into consideration per protocol. And all the old studies were done per protocol, so that means a lot of people were excluded.

So the doses were well-tolerated; that's really good news. 254 were evaluable with the modified intent to treat, and the culture results were done both with solid and liquid medium. And here's the punchline: There were no statistically significant differences among the three rifapentine arms based on their assignment to the group or the actual administered rifapentine dose in milligrams. In other words, knowing the dose told you very little about who was going to do well and who was not.

However, the high rifapentine exposure, that AUC, those were associated with sputum sterilization (inaudible). The higher the AUC, the lower number of bacilli – which is exactly what you'd expect from everything I've told you already and from all the old studies; and this has been true since 1969.

The percent of culture-negative patients was highest in the highest dosing arm, which isn't really too surprising. But it wasn't a clear trend, and it wasn't statistically significant. It was only when you really took into account the PK and the PD that you had these striking differences among the groups. And so PK/PD evaluations provided important insights, according to the authors. So the higher the AUC relative to the amount you needed to inhibit or kill, the better these drugs work.

Now, going forward for their Phase III trial, they state: "A dose will be selected that ensures most patients achieve the target AUC, especially given that TDM is not feasible in most high burden settings." So, yes, doing that in the context of a Phase III trial would be difficult; it would be challenging. However, it's not impossible. But if you look at the situation clinically, it certainly applies that if TDM were feasible, they would do it; and it is feasible throughout the U.S. and Canada and throughout Western Europe.

So as we move towards conclusion, it is not possible to give a drug for the explicit purpose of avoiding toxicity. If you're afraid to give the drug, don't give it. If you want a guarantee of no toxicity, don't give it. But if you find that you have to give the drug, then you have to accept some probability of toxicity; and not all drugs have concentration-related toxicity, including rifampin. So the best way to avoid the toxicity is

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give the most effective doses for the shortest possible time. Get there firstest with the mostest and get out.

Rifamycin efficacy is clearly concentration-dependent. It depends on the C_{max} to MIC and the AUC to MIC; and there's really no way of getting around that. The best way to achieve your endpoint is to measure the exposure and achieve the concentrations that you decide you want. You can dial-a-dose with the rifamycins and the other TB drugs. You can concentrate them inside your patient to the point where you know that you're above this MIC which, as mentioned already, was originally tied to the plasma concentrations in humans.

Now, there's always the discussion about TDM; and I'm not going to belabor the point beyond what I've done already. The decision to use it is the same as any other lab test or any other radiological test. There is no prospective randomized trial of how many CVCs with diff you should get for TB patients. There's no prospective randomized study of how many CAT scans, if any, you should get for TB patients. You get them when you need to know something.

I'll go on further and say there are no prospective randomized trials of parachutes. People just implicitly understand that, yeah, if you fall out of an airplane at 10,000 feet, you better have something to slow you down; or you're going to go splat.

None of these tests guarantees the outcome, but they all help you make a decision. And in the case of TDM, am I giving the right dose – yes or no?

Do you have to use TDM? Of course not, you don't have to use TDM. But if you keep doing what you've been doing, you're going to keep getting what you've been getting. And what is that? You're going to keep getting this. And this, in statistic terms, is an asymptotic process; we have come in at a plateau. And this hasn't changed hardly at all for over a decade. So if we keep giving the standard doses to every TB patient, this pattern is going to continue out ad infinitum; it's just not going to change. If we want to change the pattern, and we want this less than one year, we're going to have to do something different – either bigger doses or dial-a-dose based on TDM, or both.

Currently, we have an 89% effective regimen at 12 months that is not 95%; it's not 6 months; and it's certainly not 4 months. So if you do the same thing, you're going to get the same thing.

TDM is one tool; it's not the only tool. But it does allow you to individualize your therapy, and it allows you to optimize the PK/PD in your patients. And we've just proven with animal models and human models that this is the driver for efficacy. So as Ron Reagan would say: "Trust but verify." And in Russian it's "doveryai, no proveryai."

With that, I'd like to give thanks to the chemists in the lab: TJ Zagurski, Kyung Mee Kim, Emily Graham, John Kirkham; our client service person, some of you may have spoken with Roger, so it's Roger Sedlacek; and my graduate students. Now Dr. Alsultan has got not only a Pharm.D. but he's got a Ph.D. So he's Dr. Dr. Alsultan. And in the biocentrix, my pre-pharmacy students: Jon Apple, Yang Zhao and Toni Tablante.

So with that, go Gaters! Thank you.

Chuck, that was fantastic. I really, really appreciated it very, very much. And I really have to say I want to thank you for putting together what I think is an exciting topic, especially for all of us doing TB. I have to be honest with you, Chuck. This whole concept of the higher use of rifamycin is almost sacrilegious. I think you're speaking blasphemy because for all of us, we've always been trained that 600 milligrams of rifampin is the only way to go.

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So we have a couple questions I want to talk about, but I just want to bring you back to a point you made. And I just want to let you bring this point home, which is that the whole concept behind using the fluoroquinolones to shorten the regimen was so that we could get better sterilization. And if I'm hearing you correctly – and I know you didn't say it directly – but if the higher doses of the rifamycins, specifically rifapentine with Study 29 are suggesting higher culture-negative rates by two months or higher rates of sterilization, I guess – I don't want to put words in your mouth – but I guess that would suggest that it is possible that we may be able to shorten regimens using utilizing higher doses of rifamycins. Would you say that's correct?

Yeah, and that will be the focus of what will be called Study 31 from the TB Trials Consortium, which is going to be an extension of the data I just showed you – the Susan Dorman paper from *The American Journal of Respiratory and Critical Care Medicine*. That was a Phase II trial, and now they're going to roll that out as a Phase III trial to see if high doses – and it will probably be the 1,200 milligram dose – daily, with food, for patients with tuberculosis could be a four-month regimen.

Now, time will tell whether it is or if a higher dose of rifapentine or a higher dose of rifampin would be the preferred weapon. And that's a whole discussion that could be held, and it's almost a separate discussion, which rifamycin is best.

At any rate, yes, of the drugs that we know are sterilizing, we've got the rifamycins and we've got pyrazinamide. Now, the four quinolones clearly are bactericidal; but they be more like INH-type drugs, as far as their dynamics in TB patients than being like the rifamycins.

Now, the last word on that is probably not said. And, as you know, there is a high-dose levofloxacin study going on right now. So there is more to be learned about this. But at least at the doses that were given in those studies, there was insufficient added sterilizing activity from the fluoroquinolones to shorten the regimen under six months. So if you really want to have a shorter regimen, you're going to have to go with something that you know sterilizes. So you can either crank the dose of rifamycins or you can crank the dose of pyrazinamide or you crank the dose of both. And right now, the focus is on the rifamycins. That doesn't mean that the PZA issue will never be visited; but right now, we're focused on the rifamycins.

Let me ask you a question. It's kind of wild to me that with the fluoroquinolones and the four-month regimen, it made a lot of news – not only just news in the medical literature, but it actually made news in the lay public. I'm kind of interested that the results of Study 29 and the investigations really haven't gotten more play.

Well, I guess we're just going to have to try to set aside the whole Donald Trump show and try to upstage him with high-dose rifamycins. What gets into the media is always a mystery to me. I agree that this one kind of flew under the radar, at least for the general public, not for the people who study pulmonology and infectious diseases. But the general public didn't hear about Study 29X.

I've got to say to you I'm not so sure even the TB community got a lot play; I still think it's out there. And that's why we wanted to put this out there, to get people to start to think about it. And we see Dave Miller actually asked the question about this, and I agree with him. I think it's a little too early, but do you see any implications of this line of thinking? And do you see there may be some suggestions and new guidelines or anything like that – Dave is asking?

Well, the guidelines will come out; and the guidelines involve a lot of organizations, including the ACS and the IDSA and the CDC. And they're not going to stray too, too far from what's already either been approved by the FDA or has been studied adequately in a Phase III trial – unless there's simply no other data, and it's a critical question.

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So I don't anticipate that the upcoming guidelines are going to explicitly recommend routinely giving high-dose rifamycins. But hopefully, the guidelines are going to be an online vehicle in the future and can be updated, much more like the HIV guidelines or the opportunistic infection guidelines – that they come out much more frequently. As we look at the current TB guidelines, there was the 1986, the 1993, and the 2003 guidelines. And essentially, there are papers that might be published; but there are no new treatment guidelines since 2003. That will be rectified later this year, but the last published one is 2003.

And just a quick aside on guidelines, as you know, including some of the people here on the call today, several of my friends are pulmonologists or ID specialists. And those are the people who, an all-star cast, produced the TB guidelines for those three years that I mentioned – 1986, 1993 and 2003. Interestingly, as far as card-carrying members of the committees, there were no pharmacologists on those committees, even though TB treatment is essentially 100% drug therapy.

Now, if I were to write surgical guidelines maybe with some of my pharmacy colleagues, and we might write in really good English and I would use the word "ligate" a whole lot; but a surgeon reading that might say, "Well, maybe these guys aren't surgeons; they've never cut anybody."

So as pharmacologists look at the TB guidelines, they quickly pick up on things that might not be there if there were more pharmacologists on the guideline panel. That's my little editorial for the day.

I agree. The only thing I would say about that – and I agree and then I want to go through a lot of questions – but I also want to make a comment and I wonder how you feel about it. There are maybe sometimes opinions that may differ somewhat between pharmacologists and clinicians, which I think are helping. I mean, I think sometimes what we get into is sometimes you'll see recommendations that are made by one consultant; and then the clinician will come along and make another. And I think people want a black and white. I think you'd agree that without more data and more information, a lot of times this stuff is gray.

Well, I've been on enough different guideline committees. And I actually was able to contribute a small amount to the 2003 guidelines. Very specific questions were asked and I answered those, but I wasn't a card-carrying member of the 2003 guidelines committee. But I've been on other committees, for drug-induced liver disease or opportunistic infection in HIV, and I'm on the current panel for the TB treatment guidelines. And I think, especially in the past, sometimes the strongest opinion leader carried the day: "And this is what I did in my clinic, and I'm very famous."

So sometimes that influences the wording in the guidelines. And I think a quote – I don't know if it's original to Phil (inaudible), but I just love it – Phil said, "There is a fine line between dogma and dog manure."

I agree. So we have a lot of questions coming up, Chuck; and it's great. I guess John Walkington is kind of alluding to something I think that's important to bring out, which is the whole idea that one size fits all. And there are a couple of the questions where people are asking: Do you think they'll be recommending 15 milligrams per kilogram? Do you think they'll be recommending 20 milligrams per kilogram?

But I think from what you're saying, and I just want to clarify this point, one of the things that is key is that increasing the dose does not necessarily mean that you're going to increase the AUC in a totally logarithmic matter; and it's not highly correlated.

I guess the question is: Are you recommending, or are you suggesting, a two-pronged approach, both by increasing the dose – because, obviously, increasing should increase the area of the curve. But ultimately, with Study 29 (inaudible), it says the area under the curve, not the dosage, that's really making the biggest difference. Is that, do you think, a fair statement; or do you think I'm off-base on that?

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Well, David, I always think you're off-base on everything; but the statement itself is fair. So, yes, and you'll see this as the high-dose rifampin studies are published; and you clearly saw it in the high-dose rifapentine study. There is wide inter-patient variability. And that's just built in to the way your body handles rifampin, rifapentine and rifabutin. And there's no way to get around it; it's the way your body deals with that type of chemical.

So you can have tenfold, twentyfold, even fortyfold variability across the population. So if you give one dose to the person, one person might have 1 microgram per milligram as the peak concentration, and somebody will have 40 micrograms per milligram as the peak concentration. And the AUCs would move with that. So as you give a bigger standard dose, the low end of the range starts to rise.

What we'll find, I think, from the high-dose rifampin studies, is that the 1,200 milligram dose is somewhat better than the 600. And the 600 might have people that had 1 and 2 micrograms per milligram, and the high dose were have maybe 3 and 4 micrograms per milligram as the low end of the range. Rising tides raise all boats; so rising doses raises the minimum concentration, but it doesn't achieve routinely the desired concentration. So there are two different things.

I think ultimately, much higher doses of rifamycins will be used; and they might be in the 2 gram to 4 gram range. It's an unfinished story, so we just have to wait and see what happens. Nevertheless, you're still going to have that high variability from patient to patient. And, yes, you can just give them the standard dose and hope for the best; but in military terms, they will tell you hope is not a strategy. You don't say, well, I'm just going to put 1,000 guys into Syria and hope that things work out. That's not a strategy.

So if you want to know that you're hitting the target, you've got to measure it. You've got to measure something. Sputum doesn't really tell you what you really want to know because even at two months, it doesn't necessarily tell you what you want to know. You're happy if it's culture negative at two months; but they could still fail. And 20% of the patients are still going to be culture positive in two months, and they can still be cured. So it's a very inexact tool. Serum concentrations get you closer to what you want to know because it's tell you, am I hitting the target? Am I at least getting enough into the blood.

You ultimately would like to know that you could give some kind of labeled drugs, see it in the lesions of your patient; but we're nowhere near that.

And we'll get to that in a second because that, I think, is one of the issues here. But hey, Chuck, let's be honest; let's talk about the levels for a second because it's not just the expense. The other thing is that it's quite difficult to do. I mean if I'm correct Chuck, you've got to draw the blood; you've got to spin it down; and then you've got to put it on dry ice to get to you. So do you think it's only a price issue, or is it also an issue of what you need to do in order to do the levels? And is there maybe also another way or something in the horizon that may simplify that?

Well, whatever you consider difficult is going to be from your frame of reference. I've already mentioned heart/lung transplant patients. And those people have their sirolimus, tacrolimus or the cyclosporine measured all the time. They are on voriconazole, post causal – those are measured all the time. They're having all other kinds of labs done constantly, and that's just considered par for the course; and nobody really worries about that. Or if you have a diabetic patient, you're going to have them on finger sticks and glucometer all the time.

A finger stick and a glucometer, Chuck, is not spinning it down and freezing it. And let's be honest, a lot of the ones where that happens, those patients are usually in a more intensified setting, such as a hospital.

Well, it all comes down to what you get accustomed to doing. If you have a patient in a hospital or on aminoglycoside, you're not going to hesitate to check the concentrations; and that's true for vancomycin in most centers. And people don't really worry about it. If you're in a TB clinic, you may not have the lab right

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there; and it's more of a hassle. There's no doubt there's a certain hassle factor, but it's identical to drawing a chem panel. So people are very accustomed to checking LFTs and other blood tests, including the CBC with differential, in TB patients.

So the procedure itself of putting a tourniquet on and getting a blood sample is identical. What happens downstream is really not the clinician's problem; it's the lab's problem most of the time, in that the lab has to ship it to one of the laboratories that can actually measure the concentrations. Urine concentrations don't really tell you what you want to know, so I don't see them as a ready replacement. But at least across Europe and the U.S., there are multiple labs that are able to do this. I don't know all of the current prices, but I'm sure they're all more or less in a similar range of prices for the concentrations.

So, yeah, there's a hassle factor; but if you're treating without any measure of are you delivering the drug, yes or no, then you're basically hoping that your patient is "the average patient."

And I agree. I mean, I'm just saying it just to put that out there. Let me ask you another question, Chuck. (Inaudible), but the other question it comes down to, Chuck, is this; I know it's tough and we don't know, so I'm going to put it out there. Chuck, you know we do a lot of drug levels; we've been doing it for a long time. That's how, unfortunately, we got to know each other. Here's always been my question; I don't have an answer, and I'm wondering what you think.

Let's say I have a patient who now for the last six weeks has had a low level because I put him on meds for two weeks; I drew a level; it was low; I increased the dose; it was still low; increased the dose. And finally I get at 6 to 8 weeks, or let's say even 10 weeks out. Do I prolong their therapy, Chuck? Even if they became culture negative at two months, what are you recommending? Do you prolong? Do you try to get at least four months of therapy after the levels are adequate? I mean, I know the answer is – I think you're going to say that the answer we haven't found out. But I'm interested in what your approach is. What would you recommend?

Well, you're correct; you don't know. So if you look at centers where they almost never do therapeutic drug monitoring, the question is mute. They don't do the monitoring, so they would have just treated the patient however they would have treated them anyway. And then there are suggestions that patients who are very much below normal body weight, you might want to treat those longer. Those with extensive cavitary lesions, you might want to treat those longer, like to nine months. And those who are still culture positive at two months, you want to treat those longer. Those are pretty general guidelines for treating longer. But the whole focus has been on trying to treat shorter, not longer. So that's not really moving the ball forward; it's just basically losing ground if you go that route.

If you have low concentrations, personally the way I would look at it, the lower they are, the less killing that you did; and the more bugs you still have in that patient. Now, sputum samples, it's really a test of the willing. The patient has to be willing to produce, and able to produce, a sputum sample. And if either of those is not true, then you really have no measure of how your treatment is going, other than weight gain and defervescence; and those are really non-specific.

I would say it's a judgment call; it will always be a judgment call. One could argue that if you measure the concentrations earlier in treatment and then you push the doses in response to low concentrations, you get them closer to what was the average BMRC patient faster. Then if the doses ultimately become bigger, you'll get them closer to those higher doses – whether they're rifapentine, rifampin or whatever. And so I would say get to the concentrations that you want as quickly as possible.

Yeah, and just as a comment and then I want to go forward; but I agree with you. And I know in our experience, looking at hundreds of samples – we're probably over 500 in 500 different patients that were treated – the vast majority of patients who use rifampin at 600 milligrams a day will have lower-than-expected levels. And you're right. So by the time we finally get the levels up, it's usually at a time, to be

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honest with you, that the patient has already started to become culture negative. And when we really need the levels, which is early when there are the most bugs is probably when we have the most organisms.

Now, granted, I have to say the vast majority of these patients do well. But there are, as we all know, about 20% of patients who do not become culture negative within two months. And you're right; it seems that if we would start the doses higher earlier, especially right from the beginning when we need the drugs the most, when sterilization becomes the most important issue, I think we'd be better off.

I know a couple of people have asked, and I hate to say it, but: Are you recommending increasing the starting dose higher than 600? I don't think you're in the position to say, Chuck said.... But I think that more studies need to be looked at, if I'm correct.

Well, yeah, and I don't think there's going to be a guideline that says: In 2016, this is the CDC/IDSA/ATS recommendation. No, I don't expect that to be the case. But just like any drug, there are sort of off-label uses. You use drugs for non-tuberculosis mycobacteria. There are no drugs approved for non-tuberculosis mycobacteria, other than leprosy. And I'm really here referring to – well, I shouldn't say no drugs approved because (inaudible) in disseminated diseases is a special case.

But you get the point that we use drugs in indications for which the FDA hasn't rendered a judgment yet because there are insufficient data. So in this case here of if you have a patient that you want to start a higher dose of rifamycin, based on what is published – and there are published studies now for rifapentine and rifampin, and there will be more coming – then you can, as a clinician, say, I think this is in the best interest of my patient and make that call. You can do that with any drug; you just have to have a rationale for it. And it's best to document that in the charts; this is why I'm doing X, Y or Z.

But I don't think you're going to see the FDA or the CDC making a blanket recommendation for escalating the doses at this time. I think in the future they will, but I don't think they'll do it right now.

Right, and I think that's really well said. And just a couple of people – as a matter of fact, my favorite question of the day comes from a veterinarian, so I want to thank him. And he says that in animals, in his field, they never talk about a straight dose; it's always based on weight.

Again, Chuck – and I know I shouldn't have said this after I said vet – but I know I'm beating a dead horse here. But the bottom line comes down to is that it's not just about doses based on weight, but making sure those levels are adequate. I mean, that's what the studies are showing. It's really more making sure that you have a good area under the curve. And I want to make a point because the questions are coming back. We keep talking about milligrams per kilogram; but in reality, it really is making sure we, like you said, those traces – we know where we are. We know if we're hitting the target. And I think that's taking it to the next step.

Hey, Chuck, let me ask you a question here. There are a bunch of questions about intermittent therapy. And you made some statements about intermittent therapy and why you stay away. But yet, Chuck, in fairness – and let's be fair, and this is where clinicians and pharmacologists kind of butt heads a little – studies clearly show that intermittent therapy works for the vast majority of people. Am I correct?

Well there are lots of data out there, and you should look at all of the data. The so-called Denver regimen – I think that was 135 patients that were studied. So it wasn't exactly a giant study; but, clearly, it worked. And the other point is that you have a spectrum of disease. If you have a patient who comes in with minimal disease, you probably could treat him with even less than six months of therapy or with intermittent therapy; and, chances are, they're going to do fine.

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We even know that from pre-antibiotic days, roughly 20% to 25% of the patients would spontaneously cure; and about 50% would die; and then about 25% would be what were called "good chronics." They would be sick, and those are the most dangerous ones because they kept spreading it. We know that some patients, you just have to give them a nudge in the right direction; and they're going to be cured.

If you look at some review articles by Wang Wai Yew and Jacques Crosieux looking at all the different regimens, intermittent and daily – and I think Dick Menzies has done this as well – every decrement in the frequency of dose, you lose a certain amount of efficacy. So if you go from seven days a week to five days a week, you lose some efficacy; three days a week, you lose more; two days a week, you lose still more. And it's really important early in the treatment to give daily doses.

So we'll see what the new guidelines have to say about the Denver regimen versus staying for two months with daily doses. But if you don't give the drug, your AUC is zero. Now, you can still give the drug and still have an AUC close to zero because the patient can malabsorb it. The way I look at it, you heard of this in the lead-up to the Gulf War -- and I don't want to overdo these war analogies – but you heard about shock and awe. And we weren't going to just put in, like, one brigade of guys; we were going to put in hundreds of thousands of guys to deal with that problem. Then if you look at the Normandy Invasion, in one day 150,000 guys went ashore in France. So they weren't trying to just, like, play for the tie; they were going for the win.

And in TB, every dose that you give, you kill more bacilli. So you have an incentive to give more doses. And if we're going to go to a four-month regimen, it ain't going to be an intermittent regimen; it's going to be a daily regimen.

Chuck, let me stop one second just to say it's 2:30 p.m. I know that's what we were scheduled for. I want to thank everybody for joining. For those who can stay on, we're going to just do a couple more questions because, Chuck, you broke the bank here. But I wanted to just thank everybody who has to leave for joining today. And if you have a question that you want answered, if you e-mail the SNTC, we'll get it answered.

In the meantime, for those who can stay on, we have a couple more questions and points we'd like to make. We thank you for staying on.

The other thing I'd like to make a statement about is for those of you in the Southeast region, as you know, the Virginia TB Foundation has been so gracious and so supportive in putting together a grant for the Southeast Region for patients who you feel may need drug levels and you don't have a way to pay for it. We may be able to support that thanks to the Virginia TB Foundation. I just want to make that point.

I want to just, again, thank you.

But, Chuck, you're not going anywhere. I just have a couple more questions and points. Chuck, you made a really, really very dramatic statement there that you promised that it won't be intermittent. And I get it. But let's be fair here, Chuck. You talked a lot about pharmacokinetics and the patient. What you haven't really talked about is the organism and the phase of disease and the actual growth rate of the organism.

Chuck, as we know, early on you actually have organisms in the early phases of growth. And that's where it really becomes important to hit and hit hard. But as you know, Chuck, once we go into the phase where "the patient becomes culture negative" and because the number of organisms have decreased and also the places where the organisms are seeking refuge has changed, the bottom line is that the amount of time you have to hit them may change. Do you want to comment on that at all?

Well, there's the model that was proposed by Denny Mitchison and a related model by Jacques Crosieux. And so there are log-phase growth organisms; and those are the ones that are easiest to grow, and

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they're the easiest to kill because they're in full function. They're making cell wall; they're making proteins; they're doing the whole show. And we have drugs with different mechanisms of action.

So if we give four drugs, we can really attack it multiple places – kind of like we do with HIV treatments, giving different types of drugs to attack at different stages in the virus's progression. So the log-phase growth organisms are the ones that are multiplying and spreading and making more lesions because your immune system responds to it; and that results in some cases in cavitory lesions. So there are those guys, and those are the ones we can readily measure.

Then there are the ones that are purported to be in the rind in the cavitory lesions, as all this dead material, and it's very acidic; and that's where PZA is thought to work the best. And then there's the non-replicating persisters, which may be extracellular or they may be intracellular; in those non-replicating persisters, rifampin does the best job or the rifamycins do the best job at killing those.

The problem is in a given patient, you have no way of measuring that. You have no way of saying, oh, this guy's got 40% non-replicating persisters and that guy's only got 20%. It's completely opaque to us. So it's a very useful tool, and then we can mimic that in the animal models that we do or in the (inaudible) models that we do or other in vitro models. We can mimic those different stages of growth or stasis, and we can see when drugs do something or not do something. But as a clinical tool, it's really not particularly useful.

It is true that you kill with isoniazid about 0.6 logs of organisms per day for the first couple of days, and then it plateaus out pretty quickly. So you can pretty dramatically make somebody smear negative within days, if not a couple of weeks, of treatment. But that doesn't mean that bad things aren't happening and that those organisms cannot rebound and reestablish log-phase growth if you back off.

So there's absolutely no doubt that there are intermittent regimens that have shown efficacy. I'll just say wait for the new guidelines to come out, and look up the papers by Wing Wai Yew and Jacques Crosieux and Dick Menzies on the topic of intermittent therapy; and then decide for yourself.

Chuck, one of the things you talked about – and we just said it – the different phases of growth. And you know you can't talk about the rifamycins without HIV coming up. So obviously in patients who are HIV-positive, who are very, very immunosuppressed, the whole model has changed somewhat because the immune system really is not as effective in containing.

But some of the questions we have here are like: What do you think it is about HIV-positives and acquired rifamycin resistance? I mean, what do you think happened there? We're getting a couple of questions about HIV and how the rifamycins may be affected by HIV.

Well, there's nothing like an intact immune system to win the war. It is analogous, I suppose, to the situation of meningitis where it's a sanctuary state; you don't have a lot of white cells in the cerebral spinal fluid typically. And once the bugs start multiplying in that cerebral spinal fluid, they're kind of protected; not all the drugs get in there. So that's a place that is relatively immunocompromised compared to a thigh muscle or a lung, where you can easily get blood in there, easily get white cells in there, easily get drug in there.

So it's a bit of a stretch of the analogy; but nevertheless, clearly, you have patients who are immunocompromised. And there's no residual effective immune system to mop up what the drugs don't kill. In particular, if you have early in the course of treatment – the first two months in particular – of HIV-coinfected TB, and you go to an intermittent regimen at that point, every other day – I mean, immunologically there's nobody home, and there's no drugs there either. And in those cases where rifabutin was studied, you have residual low concentrations.

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Now, in vitro, if you go to a lab and you want to select rifamycin-resistant organisms, you would plate them with one-half times the MIC, one times the MIC and two times the MIC; and you would try to see what grows through that exposure to the drug. Unfortunately, with HIV-positive patients and intermittent rifabutin, that's exactly what we did; and we selected for the resistance ones. I mean, this is completely predictable.

Exactly, Chuck, and let me ask you just a comment because I know from slide 23, when they looked at acquired rifamycin resistance in the HIV/TBTC trial, the CD4 count really wasn't an issue. We did some work; we did an abstract, and I guess we should have published it. But the bottom line is when we looked at our Florida experience with acquired rifamycin resistance with like, I think, 12 different cases, even though CD4 count – you're right – really didn't necessarily come out. What did come out was extrapulmonary TB.

And we know that patients with HIV have a much higher rate of extrapulmonary TB. And it seemed like almost every one of the cases of acquired rifamycin resistance, at least we saw and still do see from time to time rarely, was more associated with extrapulmonary TB than it was actually with even intermittency. But I want to know; what do you think about extrapulmonary TB and low serum levels of rifampin? Do you think that may be a contributor? And how does penetration into other tissues affect all this?

Well, it's not as well-studied. Clearly, the guidelines would recommend for most forms of TB, with bone and CNS disease excepted, most patients can effectively be treated with a six-month regimen. So for bone, many patients treat up to nine months. For certain forms of extrapulmonary disease, where there's a lot of tissue destruction and you don't know if the drug is going to be able to get in there or not, or if you suspect there's some kind of biofilm – TB can make biofilms, like lots and lots of organisms make biofilms. Basically, there's some sanctuary within which the organisms can hide.

You have a person who may be is in their 70s or 80s, had TB a long time ago; and they come back, and they have this big, calcified rind on their [pora]; and now you have TB in there. Yeah, I mean, that's a sanctuary where the drugs might not get in; and you might have some real problems. But it's clearly not well studied, compared to the sort of garden variety, if you will, pulmonary disease.

So, yeah, whenever you think the drug is not being delivered, you're going to have to think about doing something like pushing the doses or extending the treatment.

I think you'd agree, Chuck, extrapulmonary disease in an HIV-positive individual where – because usually extrapulmonary TB is usually a very paucibacilli area. There are very few organisms. Where an HIV-positive, now not only do you have an extrapulmonary with poor penetration but I think you'd agree, these patients tend to have more organisms that would be expected to not even need higher – just like you said – levels. And I think that's where on the whole, again, I want to point out, making sure you have adequate serum levels in these cases becomes huge.

Yeah, I can't really argue the point because most of the time, we don't do quantitative cultures in extrapulmonary lesions. We don't know, routinely, what that number is. We just know it's—

Well, look, one way to do that, Chuck, is you hardly ever see a CSF with a smear positive and an HIV-negative or pleural fluid that's smear positive and HIV-negative. You see it in HIV-positive. So even though you don't have a quantitative culture, you do tend to see more smears that are positive in HIV-positive patients who are immunosuppressed.

Yeah, and they're also more likely to have positive blood cultures.

You're right.

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The other thing that comes up with this is that we now know that you grow different numbers of organisms in liquid than in solid. So there are certain forms that people expel, in their sputum anyway, that you can grow in a liquid media; then you can't grow those in solid media. And it is possible that's a response to the stressors they're under.

And in HIV-positive patients, with their immune system not working so well, they're going to have different stresses. So they might have different types of populations; so the non-replicating persisters might be in a higher number, for example. We don't really know the answer to that. But, yes, they do seem to be a different type of patient.

I agree. And then we have one more question; it's from Greg in Kentucky, our pal there.

Hey, Greg.

We all were part of this case. And when you talk about pharmacokinetics, I know it's a little off high dose; but it really does become an issue. He had a patient that was coinfecting. And the HIV physician there wanted to use cobicistat, and maybe you could talk a little about cobicistat.

The problem then was if they were going to use cobicistat, we recommended that drug levels be done because we were really concerned that the rifabutin levels, and especially the diacetyl metabolites would go high. We have actually had two cases in Florida where the combination we've used, the patient became toxic and unfortunately developed battery toxicity from it. So he was asking if you have to use these drugs, A, would you do drug levels? And if so, would you maybe use three times a week on all the drugs since you expect the levels to be high or maybe only three times a week on rifabutin or screened health? Chuck, help us here; what would you do?

Well, a lot of times you end up in situations where you'd rather not be there. But you get the patients you get; and they show up, and you have to do something for them. But I definitely do not recommend, at the outset of treatment, intermittent rifabutin. There's just too much data.

And, David, you alluded that you had maybe a dozen cases that you didn't publish? Shame on you.

Of acquired rifamycin resistance over 15 years, yeah.

Yeah, but that would be doubling the number that I already quoted that are published. So let's just accept the number you presented—

I agree with you.

There are two dozen, period. So you don't want to give intermittent rifabutin. There's not tons of data in TB patients regarding the interaction between cobicistat and rifabutin. What you can do – you don't really need to measure the cobicistat; but you could measure the companion drug, whether it's darunavir or one of the (inaudible). But nevertheless, you can measure the effector drug—

Chuck, real quick, just explain what cobicistat is for individuals who are HIV-positive.

So once upon a time, people gave boosted protease inhibitors. They used the protease inhibitor ritonavir, which by itself is hard to take at full doses. But at doses around 100 milligrams, increases the concentrations of drugs like lopinavir by blocking the clearance through the liver of lopinavir. But it also so happens to block the clearance of rifabutin. So you get a two way interaction, where rifabutin is lowering the lopinavir; and ritonavir is increasing the lopinavir, and it's also increasing the rifabutin.

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So over time, cobicstat was developed so that it has no antiviral activity; but it does block the cytochrome P450 3A4 enzyme, kind of like ritonavir did. Ritonavir has mixed effects on the other enzymes, so it's a more complicated thing to use.

Cobicstat is more selective, so it's an enzyme blocker. And because rifabutin is partly cleared by a 3A4 in its metabolism, which is usually in low concentration – it is completely cleared by a 3A4 – that if you put cobicstat in there, it's like taking the biggest football player from the University of Florida football team, putting him in the doorway of my office and saying, okay, Chuck, go out of the door. Well, it's not going to happen; there's a giant guy standing there. So that's what cobicstat does. So we have to be careful with it, but we also have to treat the patient. So you're going to give them enough rifabutin to be effective and not select for resistant, and then you check your rifabutin and HIV drug concentrations to make sure you're not really messing up one disease state or the other.

Okay, we only have a couple more minutes left so just to stay on different populations. What about rifamycins in pregnancy, Chuck? What would you recommend there? Do you have any comments on the possibility that pregnancy may affect how the drugs are either absorbed or metabolized?

Well, based on personal experience, pregnant women prefer Haagen-Dazs. But if you don't have that—

Isn't that the husbands of pregnant women? I'm not so sure; what do you think?

Clearly, the rifamycins appear to be safe for pregnancy. In the United States, we give INH, rifampin and ethambutol to pregnant women. In many other countries, they also add the pyrazinamide. And we may eventually come around to that, at least in the guidelines for pregnant women. So you generally can treat patients with TB who are pregnant the way you would treat non-pregnant patients.

As far as whether there's a profound effect on the kinetics, there does not appear to be a giant effect on this. And I think Helen McIlleron has published on this topic. She's an excellent investigator out of South Africa, so you could do a Pub Med on Helen McIlleron, M-c-I-I-I-e-r-o-n; and you could find more data about TB drugs and pregnancy.

Great, Chuck. We have a question, and one of our participants is sharing a really tough case of someone who has miliary TB and it looks like on top of chronic renal failure. And the nephrologist advised stopping the rifampin/PZA. It's kind of interesting because I think you'd agree, rifampin and PZA for the most part is really not metabolized by the kidney or at least excreted by the kidney. But I wondered in that case – and, again, there's not enough here – but I guess if the question was if the rifampin was causing an interstitial nephritis maybe you would stop. But normally, I think we would usually try to continue with rifampin/PZA in those cases. Does renal failure affect the level in these cases?

In the 2003 guidelines, I did have a chance to contribute to that section about renal failure. Normally, we don't change the dose of isoniazid, and we don't change the dose of rifampin. We have to change the dose of ethambutol. And then there were open questions about pyrazinamide. It is metabolized, the pyrazinoic acid and hydroxyl-pyrazinoic acid; but those go up through the kidneys. And we don't know for pyrazinamide whether it's the parent drug or one of the metabolites or all three that are toxic to the liver. So we erred on the side of caution and, like the ethambutol, recommended intermittent dosing of both the ethambutol and the pyrazinamide, but at the standard daily size dose, along with daily INH and rifampin in patients, for example, on hemodialysis.

Now, not knowing the whole case, I'm not sure exactly if the concern was, as you mentioned, whether rifampin was causing the kidney problem. That's pretty rare, but it is a well-published side effect of rifampin. Typically, it's in the context of a patient who has a flu-like syndrome and thrombocytopenia and renal failure. And in those patients, you stop the rifampin; and you never give it again. But that's relatively rare – not that it doesn't ever happen, but it's not that common.

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John from Tennessee is asking – you talked a little about PZA. You made a comment about PZA not providing protection against the development of resistance. First, is that correct, Chuck?

Well, it's based on the model from Mitchison and from Grosset. As we understand it, and then from some clinical data that they analyzed, it would appear that pyrazinamide essentially dresses in black and it's a Ninja. And it goes in, and it only attacks the organisms that are under tremendous stress and in an acidic environment. And an acidic environment, both in vitro as well as in people, seems to be required for pyrazinamide to be effective. So because it's at a place, a space that the other drugs may not be doing anything, and it's really not designed to protect and the data from the BMRC studies don't suggest that it protects isoniazid or the other drugs from the selection of resistance. Pyrazinamide is a drug that helps us get from the nine-month regimen down to the six-month regimen. It also seems to add to all the new drugs that are coming out. So it's an important drug, but one of the features is not protecting the other drugs from the selection of resistance.

Right, but it still plays a role. That was the second part of the question; you nailed it. If you have somebody who is MDR who is not on INH or rifampin, PZA still plays, I think you'd agree, in regimens where the INH and rifampin are not being used but not maybe in the same way as when they are. Is that correct?

Yeah, there's a great paper by Carol Mitnick and her colleagues looking at whether pyrazinamide, especially if there's questionable in vitro susceptibility, what does it contribute and where? And rather than trying to paraphrase in 10 seconds that paper, if you do a Pub Med on Carol Mitnick, M-i-t-n-i-c-k, and pyrazinamide, you will surely find that paper.

Chuck, there are a lot of people here who are writing that they're tired of your homework assignments to have to Google. And we really appreciate it; that's fantastic, Chuck. We'll go to two more questions, and then we're going to give you a break. While we were talking about special populations, you cannot talk about special populations without talking about kids. What do you think about increasing the dose on kids? If you already are thinking kids have a direction relation beyond the 10 milligrams per kilogram and goes up to 20, any data on that? Or is that something that still needs to be investigated further?

Well, Pierre Donald in South Africa has done a nice job evaluating that. So I think that the data are in on that. Little children clear the drugs much faster than adults. So their area under the curve is lower at any given dose than they would be in adults. So they need higher milligram per kilogram doses in order to get the same exposure as seen in adults. The WHO has already upped their recommendation, and you could argue that they could go higher still working in favor of the children as they tend to have non-cavitary lesions. So they tend to have, compared to adults, a relatively paucibacillary disease.

Children tend to do well. They tend to tolerate the drugs pretty well. And I think Jeff Starke is going to be giving presentations at the NAR meeting on this topic. And I think he also, along with Peter Donald, has a new book that's just come out.

And let me just make it clear. It's not just about the doses. What about the pharmacokinetics? Are you looking at the same range of like 8 to 24 to be expected levels, Chuck?

Well, the concentrations that you're shooting for are, again, relative to that MIC. So it doesn't really matter what the host is. You're really focused on the target inside of the host, the organism causing the disease. So as far as we know, the concentrations that are appropriate for adults are the same concentrations that you would try to achieve in children. But on a milligram per kilogram basis, you're going to need bigger doses in children to get there.

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Chuck, this is the last one. I think it's important because I think you made some very strong arguments, and we really appreciate it; and they were great. But we are getting a lot – are you not recommending intermittent? I think you're not in a position – the recommendations stand the way they are. There may be changes. And I think that's what your message is, that you think it's important that we go back to look at the studies about intermittent. But what would be your comment on intermittent? I know we talked about it, but I think we need to summarize it since we're getting a lot of comments about that.

As you know, in public health, a lot of patients are placed on intermittent therapy. And the vast majority, Chuck, do well. But I think what you're saying is be cautious, if I'm correct.

Yes, just specifically, in HIV-positive patients, I do not like intermittent regimens for the reasons already stated. Especially if you're using rifabutin because you're exposing them to sub-MIC concentrations every other day, and you're asking for trouble. And according to your statement, now there are two dozen cases of acquired rifamycin resistance. So don't do that.

Now, let's put aside HIV-positive for a moment and just focus on HIV-negative cases. If you have an HIV-negative case of TB, clearly there are regimens that could be used intermittently. If you ask me personally would I take an intermittent regimen, no, I wouldn't. I especially wouldn't do it in the first two months of treatment. And I think in the paper by Wing Way Yew and Jacques Crosieux – and I believe there either is one published or coming out from Dick Menzies – gets into that. You lose efficacy with each decrement in the frequency of the dose. That said, it can still be effective. And the less disease your patient has, the more likely it is that it would work.

And also at the phase of the disease, if I'm correct. Again, taking into the account the number – because when you say less disease, what you're really saying is less organisms, right?

Yeah, first there is the issue of: Is it week 1, week 6, week 10? And then how many organisms are in that patient, and did they have a big cavity or multiple cavities or no cavities? So there are two things that are working together. And so the sicker the patient, the more bugs they have, the more you need to give daily doses. I think on balance, you're best served – at least for the first two months – giving daily therapy. That's my opinion; others disagree.

We agree; that's usually it too. Normally, we try to wait until at least until the person is definitely smear negative. And if they have a lot of disease, we agree; we try to do it once their cultures are negative, if we do it at all.

Chuck, I can't thank you enough. I've got to be honest with you. With all this talk about battles and war, you definitely deserve battle pay. Having to talk to me this long is beyond what any person should have to endure. But thanks to everything you've said, I think our audience, our participants, have really enjoyed it. It's been so enlightening.

And, Chuck, I'd like to say that I could listen to you all day; but I can't. But other than that, Chuck, as always, you were fantastic. And I really want to – on behalf of everybody who has been listening – I really want to thank you.

And I want to thank all of our participants for joining today. If you have any questions, please e-mail us; we'll get it to Chuck.

Other than that, Chuck, thank you; thank you; thank you. You remain *the* Chuck.

Karen, I'm going to turn it over to you.

Thank you for another great presentation.

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Please be aware that you must complete the online evaluation by 5:00 p.m. Eastern on Thursday, February 4, 2016, if you want to receive nursing or physician credit. You will have one week to complete the evaluation.

Thank you, Dr. Peloquin and Dr. Ashkin, for a great presentation.

Thanks a lot, bye-bye now.