-- and today's moderator, Jane Moore. Jane?

Thank you, Megan. I am very pleased that we are having this webinar and discussion on this topic. I know from my discussions with others in TB programs throughout the United States that comorbidity with diabetes has become a hot-button issue as we manage those with active TB. I am looking forward to today's presentation.

I'd like to introduce our first speaker, Dr. Eric Houpt, who is a professor in the division of infectious diseases at International Health at the University of Virginia. His professional interest is in tuberculosis, and we are quite fortunate in Virginia that he is very interested in tuberculosis. He previously trained at Emory in the University of Chicago and has worked as a physician and researcher in Papua New Guinea and at the Kilimanjaro Medical Center in Tanzania. Since 2002 he has performed a number of projects on diagnostics for MDR tuberculosis at field sites in Bangladesh, Tanzania, and Thailand. He was awarded Bailey Ashford Medal by the American Society of Tropical Medicine and is an elected member of the American Society for Clinical Investigation. And, fortunate for us, he has been a tuberculosis consultant for the Virginia Department of Health since 2009. Dr. Houpt?

Hi. Good afternoon. I hope you can hear me.

We can hear you. Thank you, Eric. I'm waiting for the slides to come up and then we'll just get started. Should I try to go a little fast, given the delay? Are we going to get cut off at 2:30?

No, Dr. Houpt, we will not get cut off. You may continue just as normal as if we were starting at 1:00.

All right, I'll try to go a little fast though.

Okay.

All right. So -- all right, can everyone see the first slide?

Yes, we can see it.

All right, let's go. Thank you very much. I'm Eric Houpt and the work I'm going to present includes a collaboration with Dr. Heysell, who is currently in Tanzania, and Jane Moore, who you just heard from. So let's start with -- I want the listeners to take a guess at what percent of TB patients in Virginia have diabetes, that is to say, diagnosed diabetes, and what percent of Virginians overall have diabetes. Virginia's sort of an average state in this regard? So just curious what you think.

All right, pretty good. You're not that bad. I think we can end the poll. We see most people are saying 30% and 20%, so really feeling that there's a lot of diabetes out there. So let's keep going with the presentation and I'll come to the answer later.

So the overview of the talk is first for you to understand that diabetes increases the risk of progression to active TB. And the odds vary, depending on the study and the population, but it's about in that range, two to eight. And it's likely higher for poorly controlled diabetics. And, of course, diabetes and TB are going to increase globally, and I think that we all know that, see that, recognize that. And I'll come to the later points later in the talk. Let's just start with the first couple.

So here is a paper from the "New England Journal of Medicine." As you can see, it's 1934. And it's just to show that this association of diabetes and TB has been recognized for a really long time. This paper mentions, on the left side, that the development of pulmonary TB in juvenile diabetics occurred much more frequently than non-diabetics. And it was also commented that there wasn't any special insidiousness in the signs and symptoms of these TB diabetics. So they didn't really present differently. They were just more frequent.

The next point is that pulmonary TB developed at a very high rate in diabetic patients that had recovered from coma, diabetic coma, so a suggestion that TB was more frequent in those that had particularly poor diabetes control. And it was also recognized that the incidence of pulmonary TB was also increasing in adults. So this has been known for now at least 80 years, probably longer.

This is a study that just illustrates that comment, that there's no real special insidiousness of presentation. So, looking at a bunch of studies from all over the world, comparing the presentation of tuberculosis patients with diabetes and without diabetes, and asking whether the lower lungs were more commonly involved, were there more cavitary lesions, was there more diffuse involved in the diabetics. You can see that the studies are kind of all over the place, and there's a lot of them that say, "No." So I think the take-home point is there's not a clear cut difference in presentation in diabetics TB. There might be a little bit, but it's not as pronounced as, say, advanced HIV.

Here's another study that looks at the attributable risk of TB from diabetes and shows that it's much higher than, for example, HIV in this geographic region, which was Texas and the Mexico border. So just focus on the areas I've highlighted in red, you can see that the attributable risk of TB that can be attributed to diabetes is on the order of sort of 20%, 30%, and that's in this setting much higher than that which is attributable to HIV. Now the relative risk is higher if you have HIV than diabetes, but the point is, since diabetes is so common, that the overall population attributable risk to diabetes is very high.

And so let's look at Virginia, for instance. These are our recent data, from the webpage you can find it. And these are some standard demographic questionnaire information that we collect. And you can see, if you squint, towards the bottom underlined in red that we have about 14% of our active TB cases have diabetes. That's higher than the other sort of risk factors that are asked about. We have about 250 to 300 cases a year. So that just gives you a sense of sort of diabetes in Virginia.

And so the answer to that first question was that, in Virginia, it's about a 14% rate of diabetes in our TB patients and about 9% overall. And that's – 9% is about the national average. And this is, of course, just diagnosed diabetes, so this is self-report or known diagnoses in the medical chart. This is not a more active approach to screening.

So let's talk about screening. There's some data from India, and if you just cut to the chase, at the bottom, the number of TB patients that you need to screen with a hemoglobin A1c, so were you to just send the hemoglobin A1c on all TB patients, you would detect one new case of diabetes for every four tests you sent. So that's pretty high. And we're recommending in Virginia that our health department, if it is not known or has not been obtained, that we send a hemoglobin A1c on all new TB cases, much like we already do for HIV and some other risk factors. And, in fact, in India, for example, they recommend screening for diabetes in all new TB cases as well.

So that's sort of the first part of the talk, which just underscores that TB, and diabetes is a risk factor for the development of TB. Diabetes will probably be overrepresented in your TB population. This has been recognized for a long time. But now that diabetes is becoming so common, we are seeing it really rise to the fore as a major risk factor that we need to consider and I would recommend actively screen for.

But now let's talk about what happens when a diabetic has TB. What do we need to be thinking about regarding their TB management? So I'm going to show some information where it's been observed that treatment outcomes are worse; this is compared to non-diabetics with TB. And I'm going to talk about drug concentrations, anti-TB serum drug level monitoring. So here's a case, this is a typical case. 57-year-old Asian male with diabetes, progressive cough, found to have multifocal infiltrates in the upper lobes, no cavities, sputum smear is 2+ positive for AFB, started on four-drug therapy upon suspicion for active TB. In two weeks, the sputum culture is positive and it's probed as MTB complex. So you have the diagnosis. At about six weeks susceptibilities come back and they return pan-susceptible. And as we usually do, per guidelines, upon this result, the Ethambutol is dropped. So now it's about seven weeks into treatment and the patient is still having persistent cough, not feeling that much better. The smears are still 2+. Chest X-ray is done just to see how things are going there because he's not feeling much more and it's basically unchanged, not very helpful. Laboratories are okay. Not having hepatotoxicity.

So I have a question, just what would you do, and there's no right answer, but if we could pull up the question, here are some options. Would you do nothing, just stay the course? Right now he's on three drugs, so would you extend initiation with the three drugs that he is on and hold on switching to continuation therapy with INH and rifampin? Would you add another drug? Would you check serum drug levels and adjust the dose? Would you send repeat drug susceptibilities on the most recent culture that's positive? Or do you not really like the question or the answer and don't really -- don't buy into any of this? So let's see what you say.

Maybe this was a leading question, because most of you, by far, want to check serum drug levels and increase the dose of the drugs that he's on if they're low. That's interesting. I wasn't expecting such a dominant response, but let's keep going. We'll talk about that. And I don't really know what the right answer is, so let's see what we think.

So, first of all, the subject is outcomes during treatment for TB. So this person isn't dying, but just kind of is what we might consider sort of a slow responder. Still having persistent symptoms several weeks into treatment and smears are still positive. So most individuals, I would say, do well, but there's this subset that, in our setting, meaning in the U.S., we fortunately don't have much mortality, but we do have some slow responders.

And I think the first point to sort of emphasize is that this can be due to many things. It could be that they had really extensive disease to begin with, you know, enormous cavities, you know, individuals are going to be slower to respond. Maybe they had TB for a really long time. Maybe they have really severe TB meningitis. Then you may not have a quick brisk response. Drug resistance, you always need to think about. There could be host factors like HIV. There could be other comorbidities. Individuals that are still smoking and have bad chronic lung disease. Low drug levels are one thing that could be contributing. Diabetes could be contributing. So I think it's just important to go through this laundry list, and probably other things as well, because it's hard to say what may be going on in an individual patient, any are possible.

But let's look at some data in diabetics. So in Indonesia -- and that's a Komodo Dragon in the corner -- diabetics with TB are more likely to be culture positive at six months of treatment. That's not smear positive, that's culture positive. It's about 22%. I actually sort of highlighted in red. So that's pretty high.

In Maryland, there was a review, and the odds of death were 6.5 times higher for diabetics than non-diabetics with TB, and that's with adjusting for HIV, AIDS, weight, foreign birth, some things that could be confounders. And, importantly, many of the deaths are not strictly TB-related, and I think this is important to understand is that diabetes is a bad disease in and of itself. It often brings with it some other diseases or comorbidities, coronary artery disease, obesity, which can be associated with malignancies, chronic renal disease. And all of these things can -- you know, are bad for health. And so bad outcomes or worse mortality in a TB diabetic may be TB related, but it may be underlying disease related. Time to sputum culture conversion in this study was also a little longer but not statistically significant.

This is just a study that is a meta-analysis of several studies, mostly in the U.S., that, again, shows that all-cause mortality, and, again, I'm saying "all-cause" is increased in diabetics during treatment. And this is the study from Maryland which shows some slower culture conversion in diabetics. And, interestingly, it was seen most in individuals without cavitary disease, which is the bottom right corner, and you can see that diabetics have a lower trend line towards culture conversion, and a slower trend line.

So, okay, we recognize that individuals that have TB and diabetes may have worse outcomes. We should be more in-tune to them probably. So what can we do about it? Well, I mentioned, first, you have to think about it and figure out what may be going on because there's a long list of things that could be playing a role. And I sort of highlight them throughout this figure, and I've mentioned it. So, extensive cavities, I mentioned some host factors, you think about drug resistance. But I highlight in red the things that we can kind of do something about.

We can't really do anything about the fact that they have enormous lung cavities or presented very late. If they have HIV, of course, we can treat their HIV, and that's critical. If they diabetes, we should try to improve their control, get them on treatment. Of course, drug resistance is a whole other topic. And then low plasma drug levels are something that could be playing a role. First thing I want to say is it's not clear cut that that's the case.

This was my earlier slide, and I'm populating it with a bunch of people. So green people are individuals that have normal drug levels, and red are individuals that have low drug levels. Now, usually we don't measure drug levels in people that do well, but if we did in the studies where it's been done many will have low drug levels. If you look in the slow responders, you'll find also quite a few that have low drug levels to TB drugs. Why individuals and why so many individuals have low drug levels is interesting and raises a series of questions that I can't go into all of it.

But I just want to underscore that low drug levels do not completely explain slow response in a population of TB patients. In fact, in some studies there's no real statistically significant difference in the proportion of individuals who have low drug levels between some that do well and those that have slow response. And I think the point is there's a lot of potential issues. And so trying to ascribe the whole world of slow response to one factor is, I think, inherently sort of flawed. And so just to say low drug levels don't explain everything, but it is something we can do something about. And I would say if you look through these other things it may be worth pursuing.

So, in Virginia we have routinely been checking serum anti-TB drugs in these "slow responders" since about 2007. And this is thanks to some additional funding that we've had. It's not a routine thing. But I'll share with you some of our findings. So, first of all, it's about 14% of all of our TB patients could be categorized as "slow responders," and this is sort of loosely defined as those that don't improve in their symptoms or are persistent smear-positive after, say, six weeks.

Now, diabetics are much more likely to be in this category of slow responders, that's one of the first things that we noticed, even adjusted for some, you know, confounding or possible things that could be associated with it. And so it's about 40% of our diabetics end up being slow responders, at least that's the approximate number based on, you know, a few years of data. And among slow responders, diabetics had significantly lower rifampin levels measured at two hours. So this is sort of what the – this is looking at all slow responders, not just diabetics. But you can see that 59% have, , "low" levels of INH, and 52% low levels of rifampin. Not so with Ethambutol, a little bit, very rarely pyrazinamide. And so overall about 82% would have low levels to one or the other INH rifampin. And it's hard to predict which one in an individual patient. Some it's INH. Some it's rifampin. Some it's neither. Some it's both.

What we do is usually increase the dose one increment. And you can see that that usually does the job and raises their serum drug concentration to the "expected range." It's particularly true for Rifampin, where going up to 900 milligrams really, as you can see, brings up everybody.

Now there's a lot of reasons that an individual may have low serum drug concentrations, and I list them all here. This is sort of a standard guide. But you can see the diabetes/malabsorption is something that's on the list. The exact mechanism is not clear. It could be delayed absorption. It could be certain drug-drug interactions, although none are obvious. It could be bowel wall edema.

Anyway, this is another study from Indonesia that shows that diabetics have lower area under the curves for rifampin, like what we found but this is looking at more time points. And then this is a study, I won't really go into it, but it's just to say that low drug levels matter, at least in vitro. So if you take someone's blood, we've developed an assay -- this is Dr. Heysell in the upper right corner – where you take their blood and you incubate it with their isolates, and you can measure how well it kills their isolates. And you can measure very clearly that it doesn't kill their TB very well. And that may be seen as obvious, but it's not totally obvious, because these drug concentrations, while they're, , "low", are still above the MIC very often for the organism. So I think this, although it makes sense, is supportive that these low drug levels, you know, may actually matter.

And it brings up one question which is just what is the right dose of rifampin? So the ten mg/kg dose was somewhat arbitrarily chosen. And this is a schematic of a study that's being done in some international sites where they're looking at not just ten mg/kg but all the way up to 35 mg/kg, which is a lot of rifampin. And they're not seeing very many adverse events. The study is not complete. But they are looking at how well culture conversion occurs and how rapidly. And it really looks like there is much faster killing with the higher dose group. And so there's some other studies going on, but it would not surprise me if eventually we used 900 milligrams of rifampin routinely. We use that for some other infections, for instance. And it might be worth considering in diabetics, for instance, who may have worse outcomes.

So in 2011 we did an initiative where we started to measure just isoniazid and rifampin, and it's just these two drugs because, as I showed before, pyrazinamide is usually fine and the ethambutol is usually dropped. And we do it in diabetics at two weeks. That's about as early as we can practically do it. But if we're going to do it, we want to do it early instead of waiting for the approximate 40% to be slow responders. So we've been doing this, and this is sort of what the algorithm looks like. And I show the webpage up on the top.

So you have an individual with drug susceptible TB, let's say, and we recommend screening for diabetes first of all, and then two weeks doing this early drug monitoring. And we continue on the bottom our, you know, older strategy of anyone's who sort of not doing well after four, six weeks of treatment, we may assess drug levels for slow response. And you can see, this is what we recommend in terms of hemoglobin A1c and what we do. So if you're above 6.5 with an A1c and you're not diagnosed, we will strive to refer the client to a physician that can evaluate and provide, hopefully, diabetic care.

And so what we found with implementing this strategy was feasible. So we captured about 81% of eligible diabetics. We got them tested within about three weeks, as you can see at the bottom, about 23 days. And individuals corrected their low drug concentrations in the majority. And I'll just kind of go through these last bullet points. This is my last slide.

But of the 21 diabetics, about 76% had a low value for isoniazid or rifampin, or both. We're not surprised with this. I think it shows that we at least have a proper target population to do this in. And of the patients that had follow-up concentrations, all increased, and 12 increased to the expected range, and that included all that had low rifampin. We have in those guidelines I mention above sort of an algorithm of what we do with low drug concentrations. And functionally what it does is it shunts most diabetics to at least three times weekly therapy during continuation phase. And they end up on 900 of isoniazid and 900 of rifampin. And this keeps them to a six-month total duration, at least that's our goal in doing all this is to get them treated well, but get them treated on time because that can help. That's good for the patient and it's also good for the program.

We have not noticed major toxicities thus far, and this is not a controlled trial. But about 88% of diabetics with this early drug monitoring and pulmonary TB had sputum culture conversion in under two months, which is better than expected norms, very good. And our total statewide burden of, , "slow response" decreased a bit, and the diabetics in that group were fewer. So, again, it might limit the need for prolonged treatment and program resources.

So, with that, I'd like to thank people that I work with, Dr. Heysell, Virginia Department of Health; Jane Moore; Suzanne Keller[ph]; Debbie Thaley (ph), Denise Dodge (ph), the Virginia TB Foundation, among others, have helped support some of the drug level monitoring both in Virginia and in surrounding states. And, with that, I'd be happy to take questions.

Jane, do we have a few questions we'd like to address?

We have had a few. One was the role of nutrition, what you felt was the role of nutrition in this scenario. Is there any impact on nutrition?

I think malnutrition is something we see a lot of in individuals that slow responders. But in terms of just, you know, sheer, you know, BMI and so forth, the diabetic individuals with TB that we have are often

overweight, and so I'm not a nutritional expert. There's probably lots going on catabolically with a TB patient. But I don't have any real insight on how to, say, improve the nutrition of the TB diabetic, and I don't really know what role that plays.

And then our other question had to do with potential drug-drug interactions between medicines commonly used to treat diabetes and with the standard TB treatment.

Yeah, so, I mean any time I put someone on rifampin, you know, I do a drug-drug interaction check of all of the medicines that they're on. And there can be some drug-drug interactions with, like, some oral hypoglycemic. The direction it usually goes in is the rifampin will increase the metabolism of those and that could affect sort of their diabetic control. But for the most part actually most TB I mean most diabetes medicines, metformin and so forth, there's not drug-drug interactions or major ones that are reported. And, again, the direction is not, to my knowledge, in the direction of lowering the TB medicine. It's usually more an effect on the diabetes medicine. So to make a long story short, I don't know of any smoking guns of diabetes medicines or other medicines out there that could explain the low drug levels observed in diabetics. I think it's always good to do a drug interaction check and to be on the lookout for that, but I don't think that that easily explains the scenario.

Okay, thank you. And one last question before we switch over to the other presentation. As we've gone through this process, have we seen any acquired drug resistance as we've monitored drug levels and upped the doses? I knew before we started doing this in Virginia we used to see that periodically, but have we experienced that since we've gone to this protocol?

I would say that I have not seen it. I've heard of some cases in the past where, you know, individuals have had very low drug levels and have developed acquired resistance. I think it's rare to begin with. I think it's not even clear that you can totally ascribe that to their low drug levels. But, you know, there's some in vitro work, looking at this, that is sort of provocative and suggests that low drug concentrations within an individual can be an important driver of drug resistance. But it's been so rare that we have observed it to begin with that I don't think that we have a large enough N that we can say that by doing this we have averted drug resistance from developing.

Okay, thank you, Dr. Houpt. We'll move on now to our second presentation this afternoon from Dr. Richard Brostrom. Dr. Brostrom is a CDC Field Medical Officer, currently serving as the U.S. CDC Pacific Regional Medical Officer and Chief of the Hawaii TB Program. Additionally, he provides clinical supervision and consultation for TB control in six of the Pacific Island nations. He received his undergraduate and medical training at the University of North Carolina, Chapel Hill, and he was awarded the National CDC Service Award for his management of the two drug-resistant tuberculosis outbreaks in 2008 to present. Dr. Brostrom has published several articles regarding infectious diseases in the Pacific and has also authored a novel, "TB and Diabetes Management Standards for the Pacific." He has also served as team lead for WHO evaluation of several of Pacific island TB programs. Dr. Brostrom?

Good morning. Can you hear me this morning?

Yes, we can.

Great. Aloha from Honolulu where we actually experience the weather that is claimed by you folks in Florida and your tourist shores. I can start off by saying that I have nothing to disclose other than the fact that I've been accused of being somewhat over-exuberant when it comes to this topic of TB and diabetes. I think this is really important for TB controllers, clinicians, TB nurses, and DOT workers.

This talk is likely going to be slightly less scientific than that excellent presentation that Eric just had for us. My goal is to present some data, but also to motivate all of us to consider some real changes for our programs. So quickly going through the clock, we'll have a quick update of TB/diabetes links. Again, most of this was covered very well by Eric. And then glance at some new data from the United States. And then we'll get into the meat of the talk, which is to march through some of the best practices approach for TB and diabetes patients right now with our Pacific TB… clinical standards. And, finally, go over sort of

the specific plan, which will hopefully help us to model a move from contemplation on this important issue to some action and some real change.

Diabetes is ravaging the Pacific. In Saipan, where I lived and worked for 15 years, 70% of adults in our overcrowded hospitals had diabetes. The cause is westernization of diet, automobiles, and the desk job. But, of course, the insidious creep of the high-fat Western diet continues unabated with predictable global consequences.

The regions where TB control is problematic and areas that are currently importing TB cases to the United States every year, diabetes continues to rise the most. More than 70% of new diabetic patients in the next 20 years will come from low income countries. In India, with two million new diabetes cases every year, this endemic of TB and diabetes is present in over 20% of new smear positive TB cases. And this number is -- seems to be increasing closer to 30%. I'm going to stop here for a second. There's a comment that the voice is muffled.

Yes, we are hearing it a little muffled, too. If you are speaking on your speakerphone, it may help for you to pick up your receiver. But we are able to hear you, it's just a little bit muffled.

One moment. Let's try this. Is it better?

We're going to hear what people have to say. People are saying yes, so go ahead and keep going.

Okay, great. Now I have to do this one-handed though. All right. In Mexico the number is considerably higher, affecting 36% of all adults with TB. And in my TB clinic is the Marianas adult Pacific Islanders had a 70% increase of TB -- or diabetes among the TB cases, 70%. I just did a review of the 2012 data across the Pacific and we're close to 55% of all Pacific Islanders with TB also have diabetes. So those are not just interesting statistics; that's a call for action and programmatic adjustment.

Eric showed us just how it is that these two diseases interact. I'd like to share my two favorite studies to illustrate the topics that he presented so well. First is a study by Leung in Hong Kong. This is a study of over 40,000, the people followed for more than seven years. This is kind of a landmark study for us looking at progression from a positive skin test to active TB. And you can see that for folks who have diabetes at the end of seven years, there's a higher rate of conversion to active disease.

But when I look at that data I sort of yawn. It's not really that impressive. However, Dr. Leung did something essential here, in that when he divided the diabetics among those had A1c less than seven, and you can see that their rate of progression to active TB is actually less than people who are not diabetic, and then folks who had an A1c greater than seven, with remarkable differences with progression to active TB.

Now there's a couple points here. One is, of course, that diabetes does not cause the progression of latent TB to active TB. Poorly controlled diabetes definitely causes progression of latent TB to active TB. And a second point, just sort of a number scheme, is you can imagine that controlling A1c and driving an A1c down below seven amongst our diabetics is probably nearly as effective as six months of INH in preventing progression to active TB. Controlling glucose is really essential here.

Eric also presented this paper. This is a 2011 paper, and people that are interested in TB/diabetes really ought to download this paper and read it because to me this is the smoking gun that finally and fairly convincingly links diabetes to poor outcomes, including a relapse rate among diabetics that is measured at four times higher and an all-cause mortality rate, as pointed out by Eric, of five times higher. This is all-cause, so the point here is that these patients are fragile and we need to watch them carefully during the course of TB treatment.

When I summarize the research to various groups, I like to use this slide, my "two, three, four, five" slide which says that diabetes doubles the risk of remaining culture positive, triples the risk of progression to active TB, increases by four times the risk of relapse, and increases by five times the risk of death during

treatment. Two, three, four, five, it's so simple that even a doctor can remember that. So we've discussed the links here and some of the global data. Let's look briefly at the U.S. data.

In the last 20 years, we can see the growth in people that have diabetes across the United States each year. Interestingly, the last four categories weren't even included in the early 1990s. The possibility that there would be this much diabetes wasn't part of the epidemiology then. And I might say it's only proper that the Southeast National TB Center hosts this talk from deep in the Stroke Belt, the NCD Belt now, in the United States where diabetes is really a major problem.

What about diabetes and TB in the U.S.? Well, credit to Tom Navin's group at CDC, which is now publishing the tuberculosis risk factors that are reported amongst our cases and including them in our national 2012 report which came out last week -- the numbers from 2011. And you can see that there are almost five times more TB cases with diabetes than are reported for, for example, TB/HIV. So the effect of diabetes driving TB rates, even in the U.S., becomes apparent when we look at these risk factors. I do want to say that probably we need to add tobacco to this list. I think it's important.

The other point is that it's sort of an equal opportunity pandemic. And almost all major ethnicities are well represented when we look at diabetes reported amongst the U.S. adults, because this data is adjusted for adults only. I think, and as mentioned by Eric, it's important to talk about that this risk factor of diabetes is -- sorry, I'm also reading comments. It sounds like there's still some sound problems, is that true?

I can hear you fine, Dr. Brostrom.

Okay, well I'll press on. What I think else is important here is that diabetes sort of dwarfs the other risk factors that are listed here. And what's interesting to me is that we're not even requiring testing. This is by history only. And diagnosing diabetes by history is a terrible way to diagnose diabetes. We know that 30% to 50% of individuals have diabetes and don't know it. S unless the TB programs are testing, this number is significantly underrepresented, despite the fact that it already dwarfs most other risk factors.

I'd like to move next to the action portion of the talk and begin, again, to remind that more than 50% of adult Pacific Islanders with TB have diabetes. So in 2006, we began to address TB and diabetes in our own jurisdictions in the Pacific. It culminated in a set of regional standards of care. And our goal was to create a set of very practical, simple, realistic clinical standards to guide us towards improved care for our patients with -- our TB patients with diabetes. It's sort of based on best practices, some data, and some common sense. We found that quite useful. And although they're eight years old, they may be really the only TB/diabetes clinical standards around.

The first standard talks about screening for diabetes in persons with TB. And the rule for us is that every person with TB over the age of 18 should be screened for diabetes. We describe what constitutes a positive screen for people. Many have false positive initially when they first present with their tuberculosis and glucose result quite quickly, probably not diabetic. And we discuss a little bit how rifampin can elevate blood glucose in TB patients.

Again, regardless of the quality of the health-care system, up to 50% of people with diabetes are unaware of their diagnosis. It's a silent epidemic. So the take-home point here is that -- the question when we do an intake should not be, "Do you have a history of diabetes?" The question should be, "Can you roll up your sleeve while I test you for diabetes." That's probably the more appropriate question for us when we're screening.

In terms of best practices in the Pacific, there's tests in Saipan in the Northern Mariana Islands. And she's checking the blood glucose. Remember that tests in this picture is a TB nurse, and this photo is taken during routine TB clinic. We take blood sugar weekly for diabetes cases. It's not a research study. It's just routine care. More important than checking that blood sugar is that tests would then take the time to provide some feedback about the glucose results so the patient checking blood glucose in TB clinics creates the teachable moment that the patient needs to address their disease.

Let's stop for a poll question. This is sort of for what's happening now where you work. "When a new smear positive adult TB case is referred to your clinic for the first time what is it that you do? I would expect that most folks will check the first box, it's part of the RBCT, it's standard to at least ask the question. Okay, so while the voting continues, please just see that over two-thirds of the programs are actually asking about diabetes. It's important. And even more interested in the fact that 20% of programs are testing people for diabetes in their clinic. That's outstanding. Okay, let's move on. Thanks.

The second of these seven standards talks about screening for TB in persons with diabetes. Now the WHO framework that we put together for TB and diabetes care in collaboration calls for what we call "bidirectional screening." So that means diabetes screening in TB clinics, like we just talked about, but it also means TB screening and diabetes clinics. To do this, TB programs really need to take the lead here. And the frequency of screening is still unknown and unproven. We basically under a standard of 2.2 talk about screening to be repeated as often as the local TB epidemiology warrants. Some programs are checking what they say every six months. Most are doing every two to five years, which I think makes more sense.

When we find people that have TB infection they should be encourage to take the preventive therapy. And standard four simply says that folks with diabetes and TB should be referred for TB treatment to the local TB program.

When we looked at best practices for standards two, three, and four, we need to go the Island of Ebeye in the Marshall Islands. So here's the Ebeye TB Program checking glucose on the right. But on the left is checking TSTs in diabetes clinics. IGRAs are not available in the Pacific, nor are drug level for rifampin.

Dr. Trinidad, from Ebeye just presented some of his findings at our regional team meeting in June. The numbers are small but the impact has been large. When we look at the rates of active tuberculosis among asymptomatic individuals waiting for their metformin refill in diabetes clinics, we found in Ebeye that 5% of the diabetics had smear positive disease. This is the same rate we've seen in several published studies including, other places where TB is quite endemic. I don't think anyone's going to find 5%, but if I ask you to tell me how much TB exists in your diabetes clinic, in your states, in your jurisdictions, my guess is the answer is "We don't know." And it's important for the TB programs to jump into these diabetes clinics, to talk to those providers, either teach them how to do a skin test or an IGRA or come in as an outreach program and do it yourself to look for active disease as well as opportunities to prevent TB. Okay.

The concept of going after every person with diabetes and providing latent therapy is pretty daunting. I think we have to find a way to identify people with diabetes that are at the highest risk. And, interestingly, the data from Mexico, and even this data from Ebeye, points us towards the younger folks with diabetes as having the highest risk of progression to active TB. And combined with the study I showed you earlier of A1c levels, we might focus on individuals with diabetes who are under age 50 and with an A1c greater than eight or nine. I think in the Pacific we'll be targeting that group initially, and then we'll expand it as we get good at it managing the folks who have diabetes with latent TB. This is an important question though and the answers are not yet apparent from the research.

All right, we're closing in on towards the end here. Let's talk about treating TB in persons with diabetes, and this was really the substance of the prior talk. Standard five guides the clinicians for proper case management. We want to make sure that TB medications are properly dosed amongst TB patients that have diabetes, especially PZA and ethambutol for folks who have a diabetic nephropathy. Standard 5.2 discusses the need to observe closely for treatment failure. Often they present with a higher burden of disease and you need to be aware of poor absorption and, if levels are available, to consider drawing INH and rifampin levels.

Standard 5.3, for us in the Pacific, we called "Assure the Cure," and that is to consider extending treatment to nine months for persons with diabetes and TB, especially patients with active disease and/or delayed sputum clearance. In the Pacific the rule for most patients with diabetes is that they are treated for nine months. I know other countries treating for nine months just routinely for anyone who has diabetes, but the jury is still out on whether that extended treatment will result in a lower rate of relapse.

So diabetes is a condition that results from a clash of Western culture and genetics and poverty. And we have to be honest with ourselves that diabetes is a condition that's not very successfully managed in the Western model of the ten-minute visit every three months with a doctor. Diabetes is, indeed, a public health problem. During the course of TB treatment we have more than 100 encounters with each patient. What does that mean for us who provide TB care? Well, for us in the Pacific it means measuring and attempting to improve diabetes status throughout the entire course of TB treatment, not just at the diagnosis.

And our last two standards are about real systems change, and they're tougher to implement. They're sort of gold medal standards, standard six is, and that's to use TB clinics to help patients manage their own diabetes. In the Pacific there's a glucometer in every TB clinic. TB patients have their glucose checked weekly in the beginning and then less frequently if the diabetes is under control, at least monthly. And, more importantly, all clinic staff are reinforcing diabetes lifestyle changes at TB clinic visits. We do refer patients to diabetes clinics for long-term diabetes care and engage them into public -- or to a primary care doctor. It's important work for us.

Then we get to standard seven, which is maybe the platinum level standard, and this one just isn't for anyone. But, for me, the key element for improving TB outcomes in diabetes care is this concept of using our community DOT workers and our TB nurses as sort of mini diabetes educators. Our DOT workers are standing in the patient's kitchen delivering medications day after day. This gives us a real opportunity. However, asking nurses and DOT workers to talk about diabetes education without providing the right tools simply just cranks up their anxiety and promotes resistance to the whole concept. So I pitched the idea of a DOT-based educational tool to Kerrie Shaw of the Australian Respiratory Council. And we developed a flipchart for this purpose. It's based on a standardized approach with DOT-based education. It takes on weekly topics about TB and diabetes. It's simplified and focused. And this brief intervention is how we induce -- we try to induce lifestyle changes in the tobacco cessation world, and we felt it was appropriate for talking with folks who have diabetes. It's a great tool.

During intensive phase we start off with diabetes education -- or with TB education primarily, and then we mix the diabetes topics in second month of treatment. There are two sides to the flipchart. On the teaching side, we include text for the DOT worker to use. And the key to this tool is that our community workers avoid technical jargon, even our nurses, because that jargon is often lost on patients anyway. You'll find in here there's no discussion of glycemic index, nothing about anti-insulin antibodies, no complicated carbohydrate counts. We even avoid the discussion about diabetes medications other than to encourage pill compliance. We just take on the low-hanging fruit, portion control, moderate exercise, avoiding sugared drinks, eye and foot care. Importantly, it appears to be effective among a small numbers of TB/diabetes patients that we test at the center. The tool can be downloaded from ARC's website, which is attached to the end of my talk. And, by the way, the problem with this tool is not acceptance by the patient, they really seem to love it. The problem of course is accepting by the TB program staff.

So usually I stop here for a 15-minute favorite digression, and I'll try to do that in one minute today. And that is what do we say to the nurse -- DOT worker that says, "Diabetes? That's not my job." And to that, I remind them that there were 60 years between the time that the TB bacillus was identified and before any effective medication was discovered. In 60 years, in the West, we achieved a 75% reduction in TB mortality without a single medication. How did that happen? Well, there were multiple reasons, including economic and social improvements. One contributor was certainly the sanitarium age. Now sanitarium success was certainly overestimated. Many cured patients were simply in remission. Some sanitariums were expensive, and others were just miserable places. And their data methods were suspect at best. But we shouldn't really write off the sanitaria altogether.

The point of this picture here is that TB nurses and TB programs treated TB patients for 60 years by optimizing their health with proper diet. And, additionally, another element for TB remission was, surprisingly, moderate exercise after initial periods of forced rest. Again, TB nurses treated TB patients for more than half a century by supervising a regimen of diet and exercise. So when my talented and experienced TB nurses look at me kind of incredulously and say, "Are you serious," they're asking me to

talk to my TB patient about diet and exercise, my answer is, “Yes, that’s exactly what we’re asking you to do.”

The point is we’ve had so much success with anti-TB regimens in the 60 years after strep that maybe we’ve forgotten some of our most useful tools for TB control during the 60 years before strep, and maybe diabetes is reminding us about other ways to help augment our therapy. Okay, don’t get me wrong, I love four-drug therapy. But before four-drug therapy patients -- TB programs maximized patient’s capacity to recover with diet and exercise. Promoting lifestyle changes were the best way to treat TB, and promoting lifestyle changes were a core element of TB nursing and TB medicine. And promoting these lifestyle changes are, by far, the best way to treat diabetes today, much more effective than metformin or thioglitazones. So in Hawaii we’ve sort of set about to work towards that paradigm change. We’ve had some mixed success so far.

We started by including diabetes as a topic for all of our monthly case conference patients, and now our nurses routine report A1c and/or a glucose for all of our new cases. We then added A1c, to be drawn every three months while on treatment. And we’d like to try to follow this, and I’ll tell you why in a minute. We initiated TB clinic glucometry training so we could do the testing in our clinic. And then we advanced to the A1c point of care test that we can do in our clinic, an instant test as well, and have initiated that training. We’re doing this test in our clinic now for our cases.

Finally, we started TB clinic diabetes education training. We’ve had two afternoon sessions. We use our community partners for this. And that’s a blurry picture, almost like one of those Big Foot pictures. Sorry, but I took it with my cell phone. But here we can see the nurses sitting across from each other practicing. And this role play was more important than bringing in the professional diabetes educator as one nurse would pretend to be the patient and the other would talk about proper lifestyle modification.

The proof is in the pudding. Here’s a list of a small sampling of some of the quotes from our TB patients who have had this training. The patients are interested in it, believe me. They want to come back on their day off from work to talk some more, and we shouldn’t underestimate the value of some basic training.

Okay, let’s go to another question. This will be the last one. And I’m almost done. The polling question number two says that we begin diabetes screening and we find that 20% of our adult cases have diabetes, sort of like in Virginia. The first question was about what you’re doing today. The next question is more about what do you think -- I want you to imagine what you could possibly do. Check all the boxes that apply. What do you think is realistic for your programs going forward? We’re going to record this and send it back to you in five years, and see how we do. Not really.

I like that number at 50% and climbing regarding providing some diabetes education in TB clinics. Again, that’s a daunting concept, but we’re not talking about replacing a professional diabetes educator. We’re talking instead about just doing some real basic core nursing education. And that actually, I think, is more effective than some other complicated stuff anyway. And we stay purposefully as far away as we can from discussions about medications. That’s a whole full list there. Thank you. Let’s move on.

So we want to look at our impact. We’re almost done here. And we’re going to, as I said, measure A1c on all adult TB cases. If they have diabetes, then we measure it again at three months, at six months, and at nine months for those who are on extended treatment. And then at the same time, looking at what is our level of effort for these patients. And we want our nurses to record whenever they’re doing glucose test, whenever they do an A1c test, when they make a referral, when they provide patient education, and when they provide education during the DOT, and we just want to record that. What would we would be interested in doing here is to measure and score the patient’s diabetes control during TB treatment and then measure and score how much intervention they got from our nurses. It’s a variable effort, letting our nurses decide how much they want to do, how much they’re comfortable with.

And then the goal is at the end of 100 or so patients we want to look to see if the ones we put the most effort in are the ones that have the better diabetes control at the end of treatment, and that would just sort of justify our whole effort. If it looks like all of our efforts are not really making a difference, I think we’ll

honestly reevaluate to see whether we should try something else rather than what we're trying to do today.

Okay, you can't see me, but I'm climbing up on my soapbox now for the big finish, all right. I want to say again, you know, why should TB programs bother improving care for our TB cases with diabetes? And the answer is, because we have access, unprecedented access. We have many encounters with the patient. And this is, quite frankly, the patient's best opportunity to be motivated by a health care provider for lifestyle changes. 130 encounters is a lifetime's worth of visits to the doctor. And I don't think that we should waste this opportunity. The rising tide of diabetes amongst TB cases has to not just be under- comfortable, but incomplete pharmaceutical paradigm for standard TB treatment. Invoking this kind of change is hard, and for now there's actually a paucity of good data and some impressive stationary inertia among health professionals. But believe me, the patients are ready. So let's summarize and finish.

The short-term goal of TB/diabetes case management is to improve blood glucose during treatment, and we do this with our external partners, our regional partners, our diabetes programs, and our clinics. And using a best practices model, our goal is to effect and improve TB outcomes. But our ultimate goal goes beyond demonstrating improvements with TB outcomes. Our real measurable goal for TB and diabetes partnerships is to actually help the TB/diabetes cases achieve lifelong improved diabetes control.

As Eric said, diabetes is a terrible disease, and we can help a little, but our collaboration can only be effective if we move beyond our acquired comfort zone and provide care to the whole patient that's standing in front of us, which does improve our ability to achieve a TB cure and prevents TB relapse, but also advances us forward in the global battle against diabetes one case at a time.

So here are some of the resources that we've talked about, including the WHO collaborative framework; our regional standards for the management of TB and diabetes, that's version one, what I showed you here is more like version two, but it's mostly unchanged; and then the flipchart which is available from the Australian Respiratory Council. They've done a marvelous job where we are entering into an update to that, we think we can make it better, but it's downloadable, and we anticipate that programs will use this and copy it and make it more culturally appropriate for their setting and their own verbiage as appropriate. With that, I'd like to open this up for questions and turn it back over to Jane.

Thank you. And we certainly have had a number of questions coming in while all the conference has been going on here. One of them starts out in California and would like a little clarification on when we talk about diabetic patients being shunted to three times weekly -- okay, thank you -- shunted to three times a week regimen, do you mean to get away from twice weekly therapy, or why not do daily therapy?

Well, I think daily therapy is better. And the data that Eric showed us is troubling. When we talk about intermittent therapy, we do not do twice weekly therapy in Hawaii. We do continue to do thrice weekly therapy. And so far, our last look at our data shows that relapse rates seem to be in line with folks who don't have diabetes. But, in general, there's no good data to look at what the effect of twice versus thrice weekly is in patients who have TB and diabetes. I think the impact of a lost dose obviously in twice therapy is much more significant. So we have gone to thrice weekly therapy, which I think is in line with our set [inaudible].

Eric, I think this one is for you, because it talks about how long has our study been going on and have we experienced any relapses in nine month diabetics with six months of treatment?

The study's been going on for about a year-and-a-half, two years. I don't know if it's really a study. We call it sort of "the initiative." And we're sort of reviewing the information annually and deciding whether to continue it or not. And based on the observation that we were having a lower sort of number of phone calls for slow responders and so forth, we decided to at least keep it going for now. It seems to be operationally feasible.

In terms of the relapses, I am not aware of any. I'm not aware of very many relapses to begin with honestly. I mean I know the data on the rates of relapse, and maybe I just need to do this longer. And I

would, you know -- function of how long you follow patients. And so I think it would be too early to see. But we have not noticed it.

In terms of our practice, you know, I think we do do twice weekly a lot. And, you know, of course it's a studied regimen and it's in the guidelines, and I know some practitioners don't like the twice weekly sort of Denver regiment as much, but sometimes it's operationally much easier and so forth. And I think you need to, you know, to address things based on what your experiences are. And if you're obviously having relapses or problems with twice weekly regimens, that's one thing, but we have I think not had too much trouble with it, and so we often do it.

In terms of the shunting thing, what I mean by that is that if someone has a low -- since we're checking diabetics at an early time point, call it about two weeks, to ensure drug concentrations are within the target range, and since we find that the majority have a low level and get some dose increase, in all of those individuals we -- and you can see the details in the guidelines, but either you're up to 450 of isoniazid daily -- we're always doing daily in the initiation phase, or Monday through Friday -- or you're up to 900 of rifampin if that rifampin level is low. And then what we do come continuation is instead of doing a twice weekly regiment, we do at least three times a week in diabetics, and depending if there was a dose adjustment, we kind of factor that in. So we do 900 of isoniazid pretty much, and if your rifampin was increased to 900, then, of course, we're going to do 900 of rifampin. So that's kind of what I mean is functionally that's kind of what happens a lot is that people end up on 900/900 three times a week. But our goal is treat them in six months.

Okay. We have a related question here about if they had normal -- if for some reason we had a diabetic that had normal drug levels initially, would we consider INH 900 and rifampin 900 during the continuation phase?

Yeah, I think it's a good -- it's a very reasonable consideration. I mean I kind of personally don't really like the 600 of rifampin twice a week, just in general. But I don't have any data that really speaks to that. And if someone has sort of, you know, , "normal levels," that means they're going to be kept on their normal regimen and they're responding well, doing well to treatment, diabetic or not, there's no reason to necessarily increase the doses during continuation phase, again, since the majority of our inpatients do well with a standard approach.

Thank you. We've got a few questions, and I think I remember seeing on Dr. Brostrom's slide some questions related to LTBI treatment, such as do uncontrolled diabetics have less effective treatments with INH? And that's one. And let me find the other one here.

I'm not aware of any study that shows whether standard treatment for latent TB amongst diabetics is either more or less effective based on their diabetes. I think as we move more towards rifampin-based prevention I think that we have to be concerned about the interactions with diabetes medications and rifampin. But we still use rifampin for our diabetics, and, again, I'm not aware that latent treatment is less effective. One thing we do encourage is there's a higher risk for peripheral neuropathy and we'll do the old standard of adding a little bit of B6 in patients who are treated with INH if patients have diabetes.

Okay. Has there been any evidence that metabolic control of patients with diabetes improves the levels of anti-tuberculosis meds?

I'm not aware of anything on that topic. I think improving metabolic control in diabetes is a good thing for the patient, and it's going to be good for their TB control, you know, period. Whether it would work through drug levels, you know, not necessarily. So I would say it's a good thing, but I don't know any data on any direct link. I suppose it's possible.

Okay. Another question here wants to know about consideration for the approach to testing all diabetics for TB -- infection, I assume.

Right, and if you look at the WHO guidelines, it's still a question about what is the proper approach, what's the proper testing methodology, how often should it be done? And I think that particularly with TB and diabetes, I think we have to be mindful that this interaction is quite dependent, depending on the local epidemiology of both diseases. And a synergy seems to come at a certain level where there's enough diabetes and enough TB when you really see the interaction take off.

In terms of managing latent disease amongst this massive pool of diabetics globally, or at least in the United States, we've got to be careful. And the concept of handing out INH to everyone with an A1c greater than 7.0 or 6.5, I think, is a dangerous concept. So we'll burn up a lot of livers. We want to make sure that we're trying to focus on both the folks at the highest risk and the folks that we can programmatically handle, because it's a lot of people and this is a new effort. So that's why, for us, we're letting the data guide us, and it seems to hint towards looking at folks who are younger and folks who have worsening control of their diabetes by looking at their A1c.

So, again, for us, I think folks under 50 with an A1c greater than eight or nine, and we may just sort of try that on and see how it works. As Tony Harries (ph) from the union has mentioned several times, we're unfortunately in a little bit of a "learn by doing" mode in that I think waiting for the research is going to take a while. In the meantime, these patients are standing in front of us, and there's a lot of them. So we feel compelled to use the best practices approach and measure what we're doing, keep good track of it, and then let the research guide us as it becomes available.

Thank you. We have a question here about a range for increasing the rifampin based on weight for three times a week dosing for an elderly adult under 100 pounds. I think they're looking for the milligrams/kilogram.

Yeah, I don't have -- I would refer to the document that we put together that describes what we're doing and why we're doing it. It sounds like the nature of the question is sort of concern. You got an elderly patient who's small and maybe frail, and the concept of increasing the rifampin to 900 doesn't sit well, so, you know, I see that. I would say that, you know, I guess that's not -- it has not been, like I say, a problem of major toxicities reported, some might say that, well, if the level of rifampin in that individual that is being absorbed/measured in the blood is obviously low, below the target range, then the risk for toxicity would intuitively seem to be lower. I just say that we haven't observed problems with that. It's not to say I wouldn't also monitor that patient closely. I would also say most of the diabetics that we're talking about are not that, you know, small, frail population. So that's about what I can say on that.

Okay. Thank you. This is a question from somebody who lost audio a number of times, but I believe I have heard the answer on that. Dr. Brostrom, you also recommend either three times a week or daily in the continuation phase and not twice a week, was that correct?

Yes, that's correct. That's what we're doing in the Pacific. And, again, I don't think there's high quality data that can show that it's better than twice weekly. It's just with the drug level issues and with diabetes drugs on board, we just get nervous. So I can't say it's based on hard data, but that is the practice; that we avoid twice weekly treatment for continuation phase for our TB patients with diabetes.

Thank you. We had one question about who does Virginia's drug levels? And we sent them down to the Infectious Disease Pharmacokinetics Laboratory through the University of Florida Health System in Gainesville, Florida. I think they've just put the website up for that that you all can see right now. Dr. Peloquin also offered that if anybody has questions about serum drug levels, to go see the website. He also has pointed out that for those, Dr. Brostrom in the Pacific Islands, that they have some sort of a CDC import license or certificate and would be happy to work with you all if you wanted to see about getting any serum drug levels out of the Pacific Islands.

I think our last question is going to be is there any evidence that we have proved diabetic management in the patient's lifetime after we've completed their TB treatment?

No way. And that hasn't been measured yet, but we still haven't ramped up to give it our best effort. I think that's a -- it's the same goal that the diabetes programs are trying desperately to achieved, and it's pretty daunting. When we initially conceived of our project we were going to add an A1c drawn six months after we completed treatment. At this point, just because of our inability to control that, that's going to be a later addition to our evaluation. So, but that's what it would take is we have to look six months or a year and then draw another A1c and see if that compares well with folks who didn't get much diabetes education during their TB treatment.

You know, looking at and measuring the ability of a diabetes patient to control their disease isn't easy. It's multifactorial of course. It's pretty complicated stuff. So this is very simplistic model that we're using to see if we can have an impact, at least during the course of treatment. But in terms of long-term lifetime changes, you know, we have to sort of shoulder our load and do our part. Whether we're going to be successful in the end still remains to be seen.

Thank you. Well today we have heard about two initiatives to deal with the intersection of two global epidemics, that of TB and diabetes. Addressing the issues posed by this intersection will impact our ability to control and eliminate TB in the future. Links to the resources discussed by both of our presenters can be found within the handout, and I'm sure these will be posted on the SNTC website for future reference so that you all can get to those links.

I would like to thank both doctors Houpt and Brostrom for their informative and thought-provoking presentations today. Both of you have provided information that all of us can certainly consider and think about for implementation in our various programs across the country. Megan, are there any final instructions or reminders for our audience?

Yes, thank you so much, Jane. The Southeastern National Tuberculosis Center would like to thank you so much for joining us today. We hope that you've enjoyed today's webinar on TB and diabetes. And we'd like to remind you you'll need to complete the online survey that will be sent out to you by e-mail in order to receive continuing education credit.

If you have any continued questions regarding TB and diabetes we'd like to welcome you to please call our hotline, 1-800-4TB-INFO and we will do our best to answer your questions. We appreciate your attendance, as always, and we hope that you have a wonderful rest of your day. Bye everyone.