THE RESULTS ARE NOW IN! NOW WHAT!
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My name is Erica Lessem. I'm the Deputy Executive Director for TB at the Treatment Action Group. And we're very happy to have this webinar that's being cohosted by DR-TB Stat and ACTION. I'm going to show some slides on my screen. And also just wanted to remind people that there is also a transcript happening live of this webinar. So if you would like to follow along the live transcript, there's a link at the bottom of my screen, which I hope that you can see. And I'll make a slide show so that my slides are bigger.

So we're talking today about the implications for the field of the delamanid Phase III and the STREAM Stage 1 trial results. I'm going to give a quick overview of what we'll be talking about today. And then we have a wonderful panel of speakers.
Dr. Francesca Conradie is with us from Wits University in South Africa. We have
Dr. Carole Diane Mitnick who is from Harvard Medical School and Partners in Health.
We also have Marcus Low, who is the editor for Spotlight and formerly the policy head at the Treatment Action Campaign in South Africa. And we have Mandy Slutsker, who is from ACTION based in Washington D.C. but working globally on TB advocacy.

And we'll save lots of time for discussion towards the end of the webinar. You're all currently muted as audience members. But you'll see that there is a chat section at the bottom of your screen. And you can feel free to type in your questions there.

We're going to save the Q&A for the end to help make sure that the speakers can get through their presentations. But we'll have lots of time for questions for all of them. So feel free to just write them in the chat. And then I'll ask the speakers towards the end to share their questions -- to share your questions, I'm sorry, and for them to answer them.

So we're here today because we have some very exciting news. The first ever TB clinical trial for MDR-TB has successfully been conducted these are the first Phase III trials. MDR-TB has been on the rise for the past several years, for decades the standard of care for treating drug-resistant TB has not been based on randomized clinical trial data for the mast part. So we have these two large trials that successfully did a lot of work to build site capacity, laboratory capacity, they enrolled hundreds of patients, they followed them up for months and months, they did dozens of analyses. And now we have the results that were presented at the Union Conference in October.

This is big news for the TB field. I'm not going to go too much into the details of the

trials. But I just wanted to make sure everybody knew what we were talking about. The purpose of this webinar is really more to talk about what the implications of the results are for the field, rather than really walking through the trials in detail. But I thought it would be helpful to just give a quick overview of the design of each of the two trials that we'll be talking about to help contextualize what some of our panelists are going to say as they kind of analyze what the results mean for the field.

So the STREAM Stage 1 trial was a randomized control trial. It was an open label trial and it was a non-inferiority design, which I think Dr. Mitnick is going to explain a bit more later. But basically, it was trying to evaluate whether a shorter regimen for drug-resistant TB, which is also referred to sometimes as the modified Bangladesh regimen because it was based on a regimen that was first used in an observational study in Bangladesh. And this regimen was actually already recommended by the WHO in advance of having these trial data back in 2016.

So while the trial was ongoing, the WHO actually made this the new standard of care. But the trial was initially set up when it started back in 2012 to evaluate this shorter regimen versus the previous WHO standard of care, which was 18 to 24 months of treatment with several MDR-TB drugs. And this trial was responded by the Union with funding from the U.S. Government, USAID.

And you can see at the bottom of this slide the regimen that was used. So it was 4 months with the possibility of extending to 6, depending on culture conversion in all of these 7 drugs. And then a continuation phase with just 4 of the drugs.

So this was the STREAM Stage 1 trial.

And then the delamanid C213 trial was a randomized placebo control, double masked, some people refer to that as double blinded if you're not familiar with that term. And it was a superiority trial.

The primary endpoint that this study was designed to answer was time to sputum culture conversion over 6 months. So it was evaluating whether adding delamanid had a faster time to conversion at 6 months than just the previous WHO standard of care without delamanid.

So this trial started back in September of 2011. And it was sponsored by Otsuka, the company that produces delamanid.

This is just a really quick look at the efficacy results. As you can see in all of these, both the control and the study arm got to around 80% favorable outcome. So that means treatment completion and cure combined.

You can see in the STREAM trial, since it was a non-inferiority design, they were looking at the confidence interval. And to be able to show non-inferiority, it had to not exceed 10%. And so that's why this 11.2% is in red. Because it's out of the bounds of the non-inferior margin. And again, I think our speakers will go into a bit more detail about this.

And then the C213 trial, I showed here the favorable and unfavorable outcomes so

that you can kind of look across it in the same way that we have the results for the STREAM trial. But I just wanted to note that the trial's primary endpoint was actually not these favorable and unfavorable final outcomes. It was time to sputum culture conversion by 6 months. And the delamanid arm, the experimental arm, did have a 6 day shorter median time to culture conversion. But that was -- the P value was .0562, which means it was a little higher than what we normally want to see to show statistical significance.

So spoiler alert. What does that mean? Neither trial was able to demonstrate its primary hypothesis. But there are many buts as you're going to hear about today. And each intervention that was tested in these trials may still have utility for the field of TB. And that's what we want to explore today is, what does this mean for the field? So before I pass it over to our speakers, I just wanted to give a quick run-through of who the World Health Organization has shared with us as their plans for updating their guidance based on these results.

They have for delamanid concluded a rapid review of the delamanid Phase III trial data. They convened an external expert panel guideline development group. And now they are working based on what that group decided on a formal Position Statement that they expect to be released in January of 2018.

They noted that this is based only on Otsuka trial data. The trials 204 and 213. So a Phase II and a Phase III trial. They have not yet received any observational data from implementers. So that won't be reflected in this Position Statement that they are releasing in January.

For the shorter regimen, they plan to follow the same process as they did for delamanid. And in January, they will do an analysis of the STREAM Stage 1 interim results. But the challenge is that the trial follow-up has not concluded yet. They have noted that.

And for WHO policy plans, the consolidated guidance, as you may know, they have policy guidance for drug-resistant TB treatment in many different forms. There's the 2016 MDR-TB guidelines. There is separate guidance on bedaquiline, on delamanid, on delamanid in children. So there's been a big push for WHO to consolidate their guidelines.

They will not attempt to consolidate the 2016 MDR-TB guidelines at this point. They note that there are still data gaps. And they also noted that there's a large burden on their human and financial resources to be able to comply with the guidelines the Review Committee rules.

So they are going to do an extensive review of MDR-TB guidelines in the Third Quarter of 2018, once all necessary data are available. And this will include final results for STREAM Stage 1, the observational data for delamanid, the observational data for bedaquiline, systematic reviews on the injectable drugs. And detailed individual patient data analyses to inform the possible regrouping of second line medicines used to treat

MDR and XDR-TB. And I was just made aware that you guys could only see my title slide before. So I'll just go back and show you the trial designs since you didn't get to see those slides. Sorry about that.

So again, this was the STREAM Stage 1 trial design. Shorter regimen versus the long-term standard of care. And you can see there are 7 drugs given for 4 to 6 months. And then 4 drugs given for 5 months.

And the delamanid C213 trial was again the placebo controlled one. It was a superiority study.

I'm sorry; I'm not sure what's going on that you guys can only see the title slide. But I think we'll just go ahead with the rest of the webinar. Because those were -- I was able to talk through all of my slides. And without further ado, I'm going to turn it over to Francesca Conradie from Wits University, who has also been involved in a lot of drug-resistant TB research herself.

So Francesca, we're going to give you control and we're looking forward to hearing what your thoughts are on the shorter regimen.

>> Can you see my screen?

>> Yes, we see it.

>> Okay. I'm only -- I only have one slide to present. And that's the slide you currently can see because I'm not going to go through all results one by one.

So I'm talking about STREAM Stage 1. Before we go any further, I just want to talk about what it's like to be an MDR doctor in South Africa.

So until very recently, we implemented the long course. It involved at least 6 months of injections with other toxic drugs that if you didn't go into renal failure or go deaf, you ended up going crazy.

It -- overall through our program very little has made any impact on the outcomes of our study -- the outcomes of our program. Almost constantly between 50 and 55% of patients were successfully treated. We have a 20% death rate. And one of the -- one of the areas where we can modify pretty quickly is that about 20% of patients in South Africa are lost to follow-up. So they initiate treatment. And somewhere in their course, usually on average at around 12 months, the patients become lost to follow-up.

It's a strange thing is that they often don't appear in the data registry. So it's possible that some of those patients were actually cured. We have a reasonably good vital registry.

The medicines cost our program a lot of money. In fact two-thirds of our drug budget for the treatment of TB are occupied with the use of the second line drugs or the drugs representing TB.

So when STREAM 1 came along with the possibility of a shorter versioning, we decided to embark as a country, being one of the enrolling staff. And in fact in South Africa, almost one-third of the patients were recruited interest South Africa.

The results in the STREAM trial showed as Erica pointed out that the shorter course

did not reach non-inferiority. And as a result people think this is a failed trial. I don't think it's a failed trial because of the following reasons: The first one is from a pure cost to the program, the difference between 78 and 80% would get a reduction in almost a third of the cost of the drugs to the program. Which gives us more money to spend on other things such as contact tracing, adherence support. And I think costs to our program are very important.

But much more than that, when we unpick the data, what does it cost the patient to be on a longer course versus a shorter course? First of all, there's usually a longer period of time in hospital. And the injectables are what really limits a patient's ability to return back to normal life.

If you have to visit your clinic every single day to get a shot, then it will often end up that you can't return back to work. And I think that one of the most striking things that came out in the presentation in the Union around the short course versus the long course, around STREAM 1, was the savings to the patient. The patient spent less time and money going to clinic. Many of our patients are -- they are not wealthy individuals. And the cost of a clinic visit is significant in their budget. But much more than that they were able on average to return 1,000 hours earlier to work.

The things that really bother my patients are, when can I go back to work? I'm a single breadwinner. And I think although the short course didn't achieve it's non-inferiority, the other implementational gain that we see as a result of being able to use a shorter course is very, very important.

I think I'm not going to unpick all of the details of the trial because I know that other webinars -- it's not really my mandate to do it. But I think from an implementational point of view, although I know and acknowledge the statistical non-inferiority design and the fact that we did not achieve it, but implementation of success of the short course are so great that I don't think that it's going to change any policy in the short or long term.

Thank you very much.

>> Thank you, Francesca. That was really helpful to hear your perspective, both as a researcher and a doctor treating patients in South Africa and some of the challenges with that.

Before we go on to Dr. Carole Mitnick's presentation, I just wanted to mention for participants, sorry about the glitch with my slides. But they are now in the handouts section. There are also some other materials that might be useful for you and you might want to refer to that the speakers have shared in the handouts section at the bottom of the panel.

So we will now turn over to Dr. Carole Mitnick, who is from Harvard and from Partners in Health.

>> Hi, everyone, thanks so much for the opportunity to participate in the webinar and thanks to TAG and DR-TB Stat and ACTION for hosting it. I just want to make sure that you can see the screen that just has my -- has the display view of the slide on it.

>> Yes.

>> Okay. Not the cluttered presentation view. Great.

So I do really appreciate the opportunity to discuss this. And I'm grateful to know that many of the representatives from the sponsors and many of the investigators are on the call so that it will be great to hear their perspective on this. And particularly, if I make any mistakes in interpretation.

So I chose to answer a few questions that Erica laid out for us. The first was sort of, what is my interpretation or summary of the main findings of the STREAM trial and the delamanid Phase III trial.

And I think my first conclusion is that this is really hard. If anybody had any doubts about doing trials, Phase III trials for MDR-TB, it's really hard. And I think despite some uncertainty about these results, I think we owe enormous gratitude to sponsors, investigators, and most of all, participants in these trials.

And I guess my kind of topline conclusion or interpretation of both of these trials is somewhat technical. And it's that in both cases, there's less than 95% confidence that the trials conducted or that the experiment introduced in each of these trials provides the benefits sought.

So that is a very technical way of saying this. But I think it's really important to interpretation. And Erica already alluded to this a little bit. But I think it's good to go back to how the studies were framed, particularly with respect to the null hypothesis.

And this is just an example of the way one might think about superiority trial where risk difference is what is presented. Which was the case with the delamanid Phase III trial. As Erica noted that was a difference in time to culture conversion. So it was an interim endpoint.

So the null hypothesis was that an optimized background regimen containing delamanid results in more or less equal time to culture conversion as an optimized background regimen containing placebo. And studies always contain some uncertainty about whether or not this null hypothesis can be ruled out or excluded. And generally speaking, the bigger difference between an experimental and a control arm, the more confident we can be that the null hypothesis or the hypothesis of no difference can be excluded.

Conventionally studies aim for at least 95% confidence that the study can rule out the null hypothesis, if it's not true. And that corresponds to what we often talk about of a P value of less than .05.

So you can see in this sample slide in the top pair of lines that the confidence interval from the experimental arm, which is the blue arm, does not overlap with the point estimate, that's the dot, on the red line. And you can, therefore, conclude when you have results like that that the experimental regimen in the blue is statistically significantly superior in this case shorter for conversion than the control.

The bottom pair of lines, blue is still experimental, red is still control. But they are

dashed just to distinguish them as a pair. Shows that while the point estimate, that dot in the line, is still smaller for the experiment than it is for the control, the confidence interval for the blue overlaps with the red dot for the control. Meaning that you can't rule out the null hypothesis of no difference.

And this is sort of similar, although much more pronounced, than what we saw in the delamanid trial, which is what I'm showing on the next slide. And again, this is just about the time to conversion.

So delamanid containing regimens were estimated to affect culture conversion in 6 fewer days than placebo containing regimens.

You can see that the upper limit of the confidence interval, so for the experimental arm, the blue line, is equal to the point estimate for the control line of 57 days. The P value was .056. That means that there's only 94.4% confidence that the null hypothesis can be ruled out using the primary endpoint, the prespecified endpoint, that the company elected in consultation with Regulatory Authorities, which admittedly was a very rigorous measure of culture conversion.

They did some sensitivity analyses, which I'm not showing here, which used slightly less rigorous measures of conversion. And those sensitivity analyses offered a higher confidence that there was a difference, that you could rule out the null hypothesis in both cases over 97% confidence.

Moving on to STREAM, this is a bit more complex. One, because we're talking about non-inferiority trials -- a non-inferiority trial. And two, because the results are presented as the difference between the two. While in delamanid what was presented was the estimate and range for each.

So just another way of presenting a superiority trial results is on the left. But illustrated as a risk difference. So both -- it's a summary -- one line contains information from both studies. You're just looking at whether -- how the two studies did compare to each other in the one line.

So here in the superiority, the null hypothesis is still no difference. And the superiority is established by having a confidence interval that doesn't overlap with zero. And that's the lower line in this left hand figure.

And then in the case of not superior -- oops; sorry. In case the confidence interval overlaps with the null hypothesis or zero, then you would conclude that something was not superior.

Moving now to the non-inferiority model, which is different in that the focus is on the margin of non-inferiority. In this example and in the STREAM study, that margin of non-inferiority was 10%. And the idea behind the null hypothesis is that the experimental regimen is greater than -- sorry; is more than 10% inferior to the control.

So the objective is still similar. Investigators are looking to have 95% confidence to rule out the null hypothesis that the experimental regimen is more than 10% worse than the control. But it's no longer a hypothesis of zero difference.

So what we saw in the STREAM trial were 80.6% of patients in the control had a favorable outcome while 78.1% in the experimental regimen had a favorable outcome was that there was -- one could not conclude non-inferiority. These results would be considered inconclusive because the confidence interval actually overlapped with the margin of non-inferiority.

So -- and then I think just a couple of quick points on subgroup questions. I don't have any more slides on those. I think there's a lot of interest in what we can learn about using each of these novel treatment modalities in subgroups, including those with HIV infection. And I think the STREAM results that we saw in HIV coinfected patients do warrant some caution. Although numbers are relatively small.

I have not seen -- Francesca alluded to the economic benefits which sound substantial. I have not actually been able to see those analyses. I wasn't at the Union Conference.

Generally, in my opinion, however, the efficacy is first priority. And economics are a second priority. And that we need to use the efficacy and the strength of results to leverage changes in prices when that is really a driving factor.

In terms of what it means for the field of TB research and care that the longer regimen performs so much better and that the results maybe were a little bit less strong than we expected from the two trials, I guess I would just say it gives us lots of food for thought in future research. I think the most prominent thing is that it really enforces the critical nature of having concurrent control regimens. And concurrent control regimens that reflect the current standard of care. And I think this is particularly important in TB, where it takes so long for TB treatment to be completed and for trials to enroll.

I think there is some caution about the limitations of what we can learn through certain design choices. And really research and programmatic conventions that get reinforced. So for example, delamanid was elected to be used for 6 months of a regimen that we know lasts 20 to 24 months. So there's some question as to the -- how realistic it is to expect a long-term benefit from that when we know, say from the short course trials for drug-susceptible treatment that have demonstrated that it's pretty hard to see such an effect when a new innovation is only used at the beginning of treatment.

And we can certainly talk more about some of these lessons learned in the questions and answers, if people are interested.

I guess, like Francesca, ultimately my conclusion is that I don't think that the results of either trial indicates a real change in clinical practice. I think both studies support a sustained role for these interventions in what should really be an integrated comprehensive program for drug-resistant TB. Both interventions, both new drugs and a shortened regimen are going to be important for subgroups of patients. And considering -- programs should not consider one exclusive of the other. As we know that the shortened regimen is only indicated for patients who are -- do not have or are not suspected to have resistance to drugs in the shortened regimen.

And just to kind of give one last point on an example for both countries and WHO about moving away from one-size-fits-all approaches to the management of MDR-TB. I've just created this algorithm as one example. If people want to talk about the details, we can. But it was just a way to think about this for me the way countries might think about using the two types of interventions is starting at the top where you have the question about whether -- excuse me; you have established through a rapid test or conventional test that a patient has TB and has at least rifampicin-resistant TB. Then the next question would be whether a patient is known or suspected to have an isolette that is resistant to fluoroquinolones and/or injected or is HIV infected. And in that case then to me the approach would be to compose a conventional regimen with bedaquiline and/or delamanid.

If there is no known or suspected resistance to fluoroquinolone or injectables or HIV infection, the next question would be about Pyrazinamide, which is much harder to know at an earlier stage. But sometimes could be known that -- known resistance would also indicate a conventional regimen. I would then ask the question, what do you know about Pyrazinamide resistance among fluoroquinolone susceptible patients in whatever jurisdiction, whether that's a country, whether that's a city. The smaller the area, the better. Again, if there were a strong risk of Pyrazinamide resistance, I would say a patient might be better off in a conventional regimen.

And going down through the flow, evaluating effectively the risk through household contacts or other known contacts of having resistance, even if there isn't documented resistance in the patient in question.

And then ultimately I do not think the shortened regimen should be used in the absence of conventional drug susceptibility testing to the drugs in that regimen. Once those results are available, that should create another opportunity for a decision to either maintain the shortened regimen if there is no additional resistance documented or to move into a conventional regimen that's reinforced with new and/or repurposed drugs.

So I think that's the end of the primary points that I wanted to make about, you know, the way I interpret these results. Thanks again.

>> Thank you so much, Carole. That was really helpful to have you walk us through both the trial results and also your interpretation of them.

We will now turn it over to Marcus Low, who is the editor of Spotlight in South Africa and also a technical lead of the Global TB Community Advisory Board.

Marcus, you just need to unmute -- we have unmuted you. But I think you have to enable audio on your side. There should be like a button towards the top of your screen that looks like a microphone. There you go.

>> Can you hear me now? Okay. Sorry about that.

So yeah, thank you, Erica. I appreciate the opportunity to talk about these important trials.

Before I get going, I just want to give people some additional reading. The DR-TB Stat did a very good note on these two trials. And it's included with the materials for this webinar. And I encourage everyone to read that.

I think the first interesting point to make about these two trials are that they illustrate that I think is quite underappreciated. And that's that in TB drug development, we need both trials that get you new regimens, but at the same time we need -- excuse me. But at the same time we need trials that tell us more about specific drugs.

So these two things should ideally happen in parallel as I think these two trials illustrate. We need trials like the delamanid Phase III trial to tell us how to optimally use delamanid in constructing regimens.

So I'll say a few words about both trials. And then I'll make some suggestions for what I think we should do going forward.

Again, I think the delamanid Phase III trial is critically important in that it's the first RCT that we have of the new TB drugs. Ideally we would have had bedaquiline Phase III trial, as well. But we don't.

I think both trials illustrate that there's value in conducting large RCTs that answer basic questions. And I think we have the perfect example of that where the standard of care is compared to something new, which has now become the standard of care. And I think we need more trials of this kind that answer pretty simple questions about how do we actually treat people with TB.

So I think maybe some of us were overoptimistic. But it's hard to see the delamanid findings as anything but a serious disappointment. I think there's little -- any of it indicates that it's a break-through drug.

As Carole explained, it's on the verge of statistical significance, most of the findings. And even though it's not showing mortality benefits or long-term outcome benefits, if it was the break-through drug we wanted, then we would have seen a stronger signal there.

That said, with any drug, we have to make kind of a risk-benefit calculation. And the really positive thing about the delamanid Phase III trial is that the safety protocol is really looking pretty good. So I think on balance it indicates that delamanid is a drug certainly worth having. Certainly worth advocating for it to be registered more widely. But we should also be realistic. It's not a break-through drug. But certainly with someone with hard-to-treat TB, it's a drug that we want access to.

Regarding STREAM, again, maybe not -- I think some of us were hoping that shortened regimen would show significant -- well, would show non-inferiority but would actually do better even though statistically we wouldn't be able to say much about that. So those findings are also disappointing. I think the increased mortality in people with HIV and receiving the shorter regimen, it's an important concern. And I think when we are doing the discussion later, I would like Francesca to talk about that. Because I think in South Africa especially where we have such high HIV rates, we need to understand

what's happening there. And we need to be sure that it's not a serious safety signal.

Then when we think going forward, STREAM asked a question about the previous standard of care versus what's now become the standard of care. But the more fundamental question in TB today or in MDR-TB is what regimen should we use to treat people. And I think there's a valid question as to either -- whether either of these regimens are good enough.

Now, as you all know, there are a whole bunch of trials taking place that will tell us what the NeXT regimen should be. There's STREAM Stage 2. NeXT TB is being done in South Africa. There's NTB, TB practical. All these trials are testing the regimens containing some of the new drugs, bedaquiline, delamanid, pretomanid in some of them. But the difficulty is that we're only going to get results from these trials at the earliest late 2019 for the NeXT TB trial. So that's two years from now. And most of the other trials are going to take even longer. And I think the question we have to ask, are these two regimens in this STREAM trial good enough? Are we going to stick with them for the next two, three years? And I think the answer should be no.

It's a bit of an irony in that the standard of care performed better than what we expected in both of these trials. But it's actually still not good enough, in my view. Getting 80% treatment success in trial conditions is -- I mean, it's an improvement in what we're seeing. But it's still not good enough. And we have to understand that in programs, we'll probably not see rates that high.

So I think, you know, I would urge people not to get stuck in a fast dichotomy as to whether we have to choose between these two regimens. I think what Carole suggested as a kind of individualized care model is very promising.

What I personally feel is that we should urgently ask whether we have reached a point where we know enough about some of the new drugs like bedaquiline, to replace injectables with bedaquiline. And in that regard, I just want to refer people to another article. I think these two RCTs are critically important. And they are kind of a landmark in TB. But another really important trial -- not a trial, another really important study was published that asked the question as to whether it's acceptable to keep using injectables. So it's not an RCT. It's kind of a review of evidence. But it does what I think good science often does is to look at the evidence and just ask the basic questions. Is it acceptable to keep exposing people to hearing loss? Are the benefits of injectables that great that we should keep doing that? Or have we reached a point where you're accumulated use of bedaquiline is enough that we can replace injectables with bedaquiline?

And then finally, I think in considering these issues, a good way to think about it is if you had MDR-TB today, if you were diagnosed, what regimen would you want? And I think if we could do a poll on this webinar, I'm pretty sure none of us would want injectables and all of us would want bedaquiline as part of the standard second line or what we could treated with when we have MDR-TB.

So it's a bit offtopic. But I think there's a real risk in getting fixated on these two regimens. I think ideally we would be able to have the evidence to move forward from RCTs. But that evidence is at least two years ago away. And I think in the meantime, we can't wait. And I think there's sufficient evidence to warrant a change in regimen.

So for those of you on guideline committees or part of the WHO presence, I would urge you to at least ask the question, have we reached a point where we have a moral obligation to ditch the injectables? Thank you. I'll stop there.

>> Thank you so much, Marcus. That was a very thought-provoking presentation.

So we've had some very good overviews of the trial results and how some of the leaders in the field are interpreting them. And now we would like to turn it over to Mandy Slutsker, who is going to talk about how we can kind of combine all of these different perspectives and form a kind of coherent statement to policymakers and what we can communicate to them.

So Mandy, yeah, we can see your screen now. The PowerPoint is still just a little small.

>> I will make it bigger.

>> Thank you, Mandy.

>> Hopefully this helps. So hi, everyone my name is Mandy. I work with ACTION, which is a partnership of global health advocacy organizations that work on global health issues, including tuberculosis.

A lot of what we do is engaging policymakers, Members of Parliament, Members of Congress, and other officials on TB to create the political will needed to end the disease.

And I've had some experience leading delegations of parliamentarians. And meeting one-on-one or face-to-face in various countries to discuss a lot of things, including R&D for tuberculosis and the importance in investing in R&D. And based on that, I came up with sort of a Ten Commandments of working with policymakers that I would like to share with you today that I think could be helpful. And then I can talk through some of the questions that you might have and how it might make sense to interpret them kind of to policymakers.

So the first is just to recognize that politicians have competing priorities. And so while you spend your entire day maybe working on one issue, they have a lot of issues obviously. Security issues, economics issues, health issues, diplomacy issues. And so they don't have a lot of time. And they are not necessarily able to dive as deep as maybe you would want them to to understand everything.

The second thing would be to be concise. The quicker you can say things, the simpler you can say things, the more to the point you can be, the more they will listen. The average person has only I think certain -- I would say maybe like 6 seconds I've heard before of an attention span before they decide whether or not they are going to continue listening. And I think it might even be less for politicians.

(Chuckles).

>> Then you should explain why this should matter to them. Whatever you're sharing. Whether it's the results of a trial -- though I'm going to get into why you shouldn't share the results of a trial. Why tuberculosis should matter. Whether it's due to economic reasons, health security reasons, just the fact that they should care about people in their country and their constituents. Just explain why it matters, connect it back.

Always have an ask when you approach a policymaker. If you're telling them about, hey, there's this new drug on tuberculosis, they are going to say, so what? What do you want me to be about it? Say, it would be great if you could fund through this specific mechanism. Or sometimes just say, thank you so much for your support. Even a thank you is sort of an ask in a way. It's not an ask. But it's sort of a what you want to get from that. Just saying thank you for what you did.

Be clear about how they benefit from taking action. So if there's something like, hey, if you could vote on this, or if you could support funding for TB R&D, that will help your constituents, 30% of whom are living with HIV and, thus, at risk of tuberculosis, the leading killer of people with HIV.

Or if they live in a specific area where there is a drug manufacturer, say, this actually helps the economy in your country. Or in your region.

Face-to-face meetings are always the most effective. Using personal stories that address the problem are very helpful. So if you have personally been impacted by tuberculosis, saying, well, when I was sick, this is what my experience was. And it was very difficult every day getting injections for 6 months. And then having another 18 months of just taking these pills with horrific side effects. And now there is the opportunity to shorten the regimen and that would make it so that I could have gotten a year and however many -- 3 months of my life back. Something like that, explaining exactly why -- your personal story. And why it's -- why they should care.

Another thing is to remember that no one remembers. So even if you have met this person before, it's still helpful to introduce yourself. To explain what you do. It's helpful to kind of re-explain TB. Just because maybe you briefed that person once, doesn't mean they remember everything. Many of us are forgetful, as well.

And then I think it's also very important to be polite and respectful, even when disagreeing. Because any time you engage a policymaker, you want to be able to engage them again. While you may disagree on one thing, it doesn't mean you disagree on everything. So it's very important to keep lines of communication open. And then I would say it's very important to thank a policymaker for their time.

Now, I know this is a bit different than some of the other slides and presentations, which were on specific outcomes and perceived outcomes from clinical trials. But my best advice would be don't mention specific clinical trials to a policymaker. Many of them are not even aware that TB is an infectious diseases problem, let alone

understand a clinical trial.

And so I think the best thing to do is to talk about TB R&D overall. Or even take it a step back and talk about R&D for global health or for diseases of poverty. In the European Union there's been a lot of success talking to members of the European Parliament about poverty-related and neglected diseases as kind of a group. And getting that larger engagement. So it's not just TB but it's malaria. It's neglected tropical diseases. That kind of a thing.

Keep an optimistic tone. I think even if you're not optimistic about the state of TB R&D, if you share your lack of optimism with the policymaker, they are going to think, well, why should I waste my time on something that has no chance of ever working? So I always try to talk about it as playing the long game.

The short game is sort of like the Global Fund. Like investing in the Global Fund to fight AIDS to beat malaria to make sure that people have access to drugs that keep them alive. It's very, very important. And access to new tools. But that at the end of the day won't end TB. What will is a vaccine. But we can't get that right away. And so the investment that you make in the short term is going to help in the long term.

Now, the problem with that, from a policymaker perspective, is that in many of our countries, policymakers have term limits. They are only in office for a certain number of years. So when you start talking about something that's 10, 15 years away, that doesn't matter as much to them. It means they actually feel like they don't have the power to do anything within their elected period, right?

And they want to be able to show what they have done in order to keep getting reelected. So that's one of the difficulties with TB. Which is why it's helpful to say -- you know, talk about the investment and innovation that comes by supporting R&D. It supports economic growth. You can talk about the Return on Investment. How many lives have been saved for example with TB drugs or with ARVs. And you can talk about health security, which is something that a lot of people have been interested in with regards to antimicrobial resistance. I always talk about how tuberculosis is the only drug-resistant disease spread through the air. And that makes it very dangerous. And it's important for everyone to work on this. Because anyone can get TB. And it threatens our economy, it threatens our lives. And talking about pay now to save later.

There's been a lot of really great work done by the Global TB Caucus and the AMR Review that shows that investing now can actually save money over the long run. And that lack of investment is actually -- it will cost the world $1 trillion by 2050.

So just like the importance of talking about -- I know it always sounds -- I'm trying to think of the word like almost dehumanizing or not -- but just talking about money. But that's something that's always on the forefront of many policymakers' minds. Many of them are involved in crafting budgets. So talking about investments and how investments pay off is helpful.

And as you know, with R&D, you have to figure out what works and what doesn't.

And if a clinical trial fails quote-unqoute, that doesn't necessarily mean that it was a waste of resources. It means, well, this isn't how we're going to solve that problem. Now we know this isn't how we solve that problem. So we can move forward and try something else.

And then finally I will share with you the global technology -- the Global Health Technologies Coalition has a great Web site where they have a lot of specific guidelines for engaging -- not guidelines for engaging policymakers. But a bunch of facts that talk about funding-neglected diseases, investment in R&D. Talking about the Return on Investment in terms of lives saved, economic growth, cost savings and health security. And I think it's just these sort of infographics can be quite helpful when talking to policymakers.

And I know this is quite different from what the other presentations were. But I'm happy to answer any questions about this.

>> Thank you, Mandy. I think it's helpful for us to think about as we've gotten very down in the weeds thinking about the trials and their results and what the implications are for the field to keep in mind that at some point we will need to kind of come back out of it and have a message that we want to ask our policymakers about what the best kind of care that we should be able to provide for people with TB is.

So we do have a lot of time now. We're coming up on an hour. But the webinar was reserved for an hour and a half. So I hope people will be able to stay on and send their questions.

There's a chat feature at the bottom of your screen. So feel free to type in a message. Just make sure that you either send it to the organizers or to me or the entire audience so that we'll be able to see what your questions are. And so folks in the audience, you can start sending those in.

But while people are thinking of their questions, I would love to just go through with the different attendees, Marcus had the suggestion that we could do an informal poll of, you know, what treatment people would want to take if they were diagnosed with MDR-TB. So I would love to start with just a quick run-through of the different presenters. And ask them to answer that question.

If you were diagnosed today with -- let's say you had a gene expert test and were positive for rifampicin-resistant TB, what regimen would you want to be started on? And if there are any other conditions under which you would want your treatment to happen, if you could specify that, that would be great.

So I'm going to put the panelists on the spot. Francesca, if you could unmute yourself and answer that question, that would be great.

>> Sure. You really put me on the spot in a really short amount of time.

I think that when we look at the mortality benefits of adding the new drug, particularly with the new drugs, and in particular bedaquiline because we don't have it yet for delamanid, is I would like to have a new drug in my regimen. If possible, I would

like to not have to take an injectable. So although -- if I had an option, I would like to be randomized with no injectable and bedaquiline in STREAM 2.

>> Great so you would take a shorter regimen with bedaquiline without an injectable in an experimental condition?

>> Yes.

>> Okay.

>> All of the blood tests and cultures being done regularly.

>> Great. Thank you for doing this exercise.

Carole?

>> This is a great -- it's a great question. And I think it's a good highlight to what we need to pursue in terms of equity. So I would -- would be a little more radical perhaps than what Francesca said. I would like a regimen with bedaquiline, delamanid, linezolid, clofazimine and levofloxacin for 9 months. And then I would like to be followed very carefully obviously during the treatment for toxicity and also for 6 to 12 months after for recurrence.

>> Great. So much more -- a combination of newer drugs and for a shorter period of time without an injectable?

>> That's correct.

>> Marcus, let me unmute you. Oh, you're unmuted but you just need to do it on your side. I think you just need to -- there's a button towards the top that has like a microphone.

>> Can you hear me now?

>> Yes.

>> I would go with the -- with Carole's regimen. I would be willing to risk linezolid, obviously providing that I'm being treated by a very good facility and by a good doctor. I think what's possible more broadly may be different. But yeah, personally, bedaquiline, linezoilid injectables.

>> Great. And Mandy, what about you?

>> I honestly don't know if I know enough to answer that question.
(Chuckles).

>> With regards to the specifics. But I do echo what Marcus said about the importance of how you're treated. And just would like to make a plug for the importance of psychosocial support, nutritional support, so that each person is treated for not just medically but what they need to get through the whole allotted period of treatment.

>> Another great point. Thank you. Okay. So I'm going to go through some of the questions from the audience now. We have a question for Francesca.

Can you comment on how comfortable you would feel putting an -- sorry; as an MDR-TB doctor putting someone living with HIV on the shortened regimen?

>> I'm unmuted?

>> Yes.

>> As an MDR -- as a STREAM trialist, I would have no hesitation putting an HIV-infected individual on to the short course. And then of course what we need to treat patients successfully is early diagnosis of HIV and early initiation of appropriate antiretroviral therapy.

Unfortunately the combination of TB and HIV, particularly HIV -- advanced HIV is a toxic combination. But no, I wouldn't have a hesitation. I think it is a tough ask to punish -- and I'm using an emotional word on purpose -- everybody who is HIV infected to commit them to a long course just because of the type of findings in one study. And those findings are best in small numbers and are not statistically significant.

>> Thanks, Francesca.

There's a question from Nimer from the Damien Foundation for both Carole and Francesca. How do you explain the difference among the STREAM results and the global TB report 2017 success rate for the shorter treatment regimen?

So you know, the fact that we are seeing about 85% success rate for the shorter regimen, according to what's in the global TB report. Maybe Francesca, you could take a stab at it and then Carole.

>> Yeah, well, I think that the estimate is between 78 and 85 are pretty close. And I would have to see the confidence intervals around them to decide if there's any difference.

>> Okay. Carole?

>> Yeah, I would echo what Francesca said. I don't know how meaningful that apparent difference is. Maybe another way of thinking about it, though, is the apparent difference between the results and in the observational studies that reported 85, 90% and the results in the experimental arm of the STREAM trial.

And I think there are a couple of possible explanations. So one is the way the outcomes were defined it's a more rigorous outcome definition in the STREAM trial than in routine programmatic care. Two, obviously is the trial effect. And that's probably part of what's resulting in the increase response among patients in the control arm, as well. And then the third possibility is just that the population is not as restricted in the STREAM trial. That there are more patients with perhaps resistance to drugs in the shortened regimen and other co-morbidities that might worsen outcomes than had been the case in the cohort studies. And that's something when we see more subanalyses, we might get somnolence into.

>> Interesting. And Carole, another question for you. This is from Ruvandhi. What is the significance of considering the PZA resistance in the algorithm that you showed for treatment?

>> I think there's a lot of -- there continues to be a lot of uncertainty about the importance of PZA resistance in treatment of MDR-TB generally and in the STREAM -- in the shortened regimen in particular. And I think -- I've singled it out because one, it's not available through -- you can't do PZA testing through routinely available rapid

molecular tests at this point. And we do know that at least among sort of all-comers for MDR-TB treatment, that Pyrazinamide resistance is present in about 50% of the isolettes of those patients. It's probably a lower proportion when you exclude fluoroquinoline resistance, which is one of the criteria for inclusion in the STREAM regimen or in the shortened regimen. But I think until I have evidence from a larger number of patients that Pyrazinamide resistance does not compromise the shortened regimen, I wouldn't want to use it, if I had PZA resistance. I'll put it that way.

>> Thanks, Carole.

So there was a question from Ruvandhi in terms of implications for practice in the field. There seems to be discrepancies between Francesca and Carole regarding how the shorter regimen should be used. Also, access to -- what about expanding access to repurposed drugs like linezoilid and clofazimine?

So Carole, maybe you can take a first stab at that about how far the shorter regimen should be used. And the use of repurposed drugs like linezoilid and clofazimine.

>> Sure; sure. And I would invite Marcus to participate in this, as well. And Mandy, if she feels like she has something to add.

I guess what I would say is fundamentally I think that the shortened regimen was originally tested in and the STREAM inclusion criteria continued in this was originally tested in what was intended to be fairly simple MDR, if you will. And I think there's some debate about what simple MDR is, if it's resistance to isoniazid and rifampicin only or resistance only to first-line drugs and not second-line drugs. But the point is in patients who had very -- who had no prior exposure to second-line drugs and who have little risk of having resistance to the drugs in the regimen. And my sense is that when those criteria are strictly adhered to, the regimen performs quite well. So I would support its use in those populations in the context of a program that has options available, different options available, for patients whose resistance patterns or treatment history don't meet these criteria.

And I think there's been a real -- there's been a palpable shift toward the shortened regimen away from the use of new and repurposed drugs by countries since the WHO guidance was released last year. And I don't think that's appropriate. I don't think it's one or the other. I think to have any impact on the epidemiology of MDR-TB not to mention not doing the best for those patients, I think both alternatives need to be available.

The repurposed drugs, it's hard to answer that in Broadway. I mean, we -- Marcus talked about the virtue of trials or studies that answer simple questions. And I agree completely. Those are extremely valuable. And I also believe that we need more trials that help us to answer some of these more complex questions, like what is the best way to integrate linezoilid and clofazimine as the most commonly cited repurposed drugs into regimens and to optimize the efficacy and toxicity balance. So I think there's still more work to do on those. But I also agree with Marcus, in the interim while we're

waiting for the results of the aforementioned trials, we have to keep trying to improve on what are the current standards because they really are not good enough. And I think new drugs and repurposed drugs are part of that picture.

>> Thanks, Carole, Marcus, I'm going to unmute you. Do you want to add anything to that? You're still muted on your side. If you want to speak -- there you go.

You're still muted.

>> Can you hear me now?

>> Yes.

>> I don't have much to add. I mean, personally I'm kind of conflicted myself. Because I am quite -- let me put it this way, I have a lot of sympathy for Francesca's position. I think -- I'm not sure we have good data on this. But I think as a patient, I definitely would prefer 9 months to 24 months, even if the chances of cure are slightly lower.

You know, these things are tricky. It's a big operational question. And changing guidelines, filtering it through a system while you're trying to decentralize care, et cetera, it's a complicated care.

So you know, that's -- I think for me what that means, it's actually a reason to maybe skip a step and to think, what is the next thing? Because you know, I'm quite confident that guidelines will change before we get the next batch of evidence. So we might as well change it as counterintuitive as it feels to change the guidelines while we have all of these outstanding RCTs that are still going on. Thanks.

>> Thank you, Francesca, did you want to add anything in response to the question about, you know, either the use of the shortened regimen or the expanding the use of repurposed drugs like linezoilid and clofazimine.

>> Well, clofazimine is of course expanded use of a repurposed drug. So we are starting to accumulate the evidence.

In our research is the same as where we were in my mind in HIV research in the year 2000. We had drugs that saved peoples' lives but also had some pretty revolting side effects, including lactic acidosis, which could have been fatal. We didn't stop rolling up into antiretroviral therapy because of that. We had a parallel research agenda. And as the new drugs were registered, we slotted them into programs.

So I think where we are now is a bit uncomfortable. And I don't think the results from STREAM 1 are the answer to the world's MDR-TB problem entirely. We need to find a way of getting rid of injectables if possible. STREAM 2 is doing that. Using a safe Akron lone. In our current regimen in the current protocol, they use moxifloxacin and a number of patients whose QT went above 500 is a concern in terms of monitoring at a program level.

So we must think about what we can do to make this -- to build the next step, to make this regimen safer.

>> Thank you. And a follow-up for you, Francesca, from u was that she noted that

you did not choose the NeXT regimen as to what you would want to take if you had rifampicin-resistant TB, despite the NeXT regimen's excellent early results. Can you comment on that?

>> So the NeXT regimen is a combination of three novel agents. And the biggest question around the NeXT version is what dose of linezoilid do we use and the NeXT investigator. And I think I'm probably slightly more afraid of linezoilid side effects than I am of kanamycin side effects. So both of them are pretty toxic drugs. I think the standard MDR I'm not sure that the risks are worth the benefits of the NeXT regimen. If I had pre-XDR or XDR, the NeXT would be the one I choose. Once you move, then you start to -- then the prognosis really changes.

>> Thank you. This is a question from Debra Bombay. She is asking, should we exclude patients with resistance to ethionamide or high dose isoniazid for the shorter MDR-TB regimen? She notes the previous understanding was that if the patient had resistance to either ethionamide or isoniazid, they still qualified. So maybe Francesca and Carole could take that one.

>> So the way that the NeXT regimen -- sorry, the way that the STREAM regimen was designed, it didn't matter which mutation you had for isoniazid, you would be covered. So if you had the katG mutation, then ethionamide would be the drug that would cover. Or if I have INH mutation, then high-dose INH would cover. So either way, we couldn't drop either of them.

In South Africa we have the privilege of getting to see our assays and be able to access them clinically. If the INH mutation is present, there is no point in continuing with ethionamide because it is a poorly tolerated drug. So we drop it in South Africa. But that's only because we have access to the results. In countries where you don't have access to those results, you need to continue both. And we continue INH irrespective of katG, presence or absence. I know this is getting into technical detail. But that is the way that the regimen was designed.

>> Okay. I think that is helpful for answering Debra's question. And so when you drop the ethionamide, you still continue with the shortened regimen or do you switch them to a longer conventional method if they have that resistance?

>> No, we continue with the shortened regimen. The INH mutation has complete resistance to ethionamide so there's no point in continuing with that drug. You're giving a drug that's got lots of side effects and is not working. And in the proportion of patients that I'm sure when we get the analysis results from STREAM, we'll know which one everybody belongs to. But there's no point in carrying on. There's much more debate about the efficacy of INH in the presence of mutations. And so that's why we don't stop. INH is a much better tolerated drug than ethionamide.

>> Great. I think you answered that pretty thoroughly so we can more on. There's a question from Aung Si Thu. She's referring to Carole's presentation.

There's a flow diagram. And it shows that adding bedaquiline or delamanid in the

conventional regimen is it that it can reduce treatment duration or increase treatment success rate or any benefit? So Carole, maybe you could just talk about your diagram, why you thought that bedaquiline or delamanid should be added to the conventional regimen.

>> Sure. I think at this stage, it would be added to the conventional regimen of the conventional duration. And I think this is, you know, an area ripe for research, as Francesca and Marcus have alluded to on multiple occasions of thinking about when is enough enough with being able to replace an injectable with bedaquiline. And you know, as we know, it happens quite a bit clinically in patients with toxicity to the injectables.

So I think that is a possibility that programs could consider under operational research conditions. And, you know, I think it would also be another opportunity for operational research to look at shortened regimens.

But we just -- with one of the novel and/or repurposed agents. But we just don't have the data on which to make those recommendations at this point. So basically kind of drawing the link between the guidance for the use of bedaquiline and delamanid to that of the exclusion criteria for the shortened regimen. And more or less anybody who is not eligible for the shortened regimen is at increased risk of poor outcomes on MDR-TB treatment. And therefore, is eligible for delamanid and possibly also for bedaquiline.

>> Thank you. We have a question from Kathy Hewison. She notes that the WHO does not advise changes to the shortened regimen. But she says most people would agree that the injectable could be replaced by bedaquiline in case of adverse event or risk of adverse event. Would you agree? I'm going to ask all of the panelists this one.

Would you agree that you could replace bedaquiline with an injectable in the case of an adverse event or risk of adverse event in the shortened regimen.

>> In the case of an adverse event particularly hearing loss, the answer is yes. But it's the same requirements as for entry into the short course regimen. And that is that you're dealing with pure MDR. So resistance or the rifampicin-resistance or rifampicin-resistant INH. But anything more than that with the fluoroquinolone or an injectable, I think you can't -- you would have to add other drugs to that regimen.

>> Great. Carole?

>> Yeah, I agree with Francesca. I don't think we have any evidence to suggest any other way of managing it.

>> Marcus, would you also like to take a stab at that one? I'll unmute you although I think you're still muted from your side.

>> Can you hear me now?

>> Yes.

>> Yeah, I mean my view is that anyone who takes an injectable is at risk of a serious adverse event. And I think we -- at the time we have systemically undervalued the seriousness of hearing loss and what that does to peoples' quality of life. And I think

that continues. And I think that's inherent in the current guidelines. That the severity of that side effect is underappreciated. So you know, my reading would be that everyone should get -- as a matter of course, everyone should get bedaquiline instead of an injectable.

>> Great. I'm going to take my moderator privilege and ask everybody a question. Because, you know, one thing that I haven't heard very much come up in today's webinar is the importance of access to drug susceptibility testing. Francesca mentioned a little bit about having results in South Africa really helps them manage care. But in the U.S., where I live, the shortened regimen really isn't even on the table for discussion as an option. Because they do full DST workup on everybody. And they wouldn't -- a clinician wouldn't want to put somebody on this kind of standardized regimen that has a lot of drugs in it. Some of which are not particularly effective. And all of which bring some side effects.

So here they would much rather, you know, do the full DST workup and do an individualized regimen. But of course that's only possible if you have quick access to DST.

And I was wondering if Carole and Francesca might be able to speak to challenges around diagnosis and the importance of it. And maybe just some of this dichotomy that we're seeing in the field where some people are really wanting to move towards a standardized regimen to make it easier for patients. And then on the other end of the spectrum, we see a real push for highly individualized medicine.

So I'm wondering if you guys can comment about those two big topics.

>> So sorry, Erica. When you say two big, you're talking about, one, access to accessibility testing and, two, about the standardized versus individualized?

>> Yes.

>> So yeah. I, as a principal, tend to shy away from dichotomies. Because most of them, at least when we're talking about access issues, tend to be linked directly to access to resources. So I -- again, I think my approach would be a sort of hybrid that does integrate all of the tools available for patients. And that includes using, for example, this decision in a program algorithm about whether somebody is going to go down the shortened regimen path or going to go down an individualized regimen path. That should be a lever to increase access to diagnostics and increase the ability for clinicians to have the information from those diagnostics as Francesca was describing to guide decision making.

So I just -- you know, I think among the 600,000 new MDR-TB cases annually and the prevalent whatever, 1.2, 1.8 million, a single approach is not going to make an impact on the burden of disease. And so I think that all of these -- all of the tools need to be used and the leverage that comes from, say, having new regimens needs to be applied to access to new diagnostics and vice versa.

>> Thanks. Francesca, could you comment?

>> So working in a country that has a high burden of MDR-TB, we require some way of being able to plan what drugs we need to order and how many of them we need to order.

If it's not -- it is a pity that it's sort of separated into the high resource countries get everything and the low resource countries get very little. It is -- I think we need a pathway -- I mean, somewhere in between the two. When a patient presents really ill, do we -- how long do we wait before we get everything back? And how well can we rely on the tests anyway?

So it's -- there isn't a simple answer. In an ideal world, we should do a whole genome sequencing on everyone who has TB and standardize observation according to that. But in the volumes we're seeing in South Africa, that's not possible.

>> Thanks, Francesca. How about you, Marcus; do you want to comment about that?

>> I fully agree with Francesca. It's -- I mean, it's a matter of what's possible within a highly constrained health care system.

>> Okay. We have a few more questions. And we have about five minutes left on the line. So Miriam had a good question. We haven't talked much about delamanid in this discussion section, even though it was one of the trials we reviewed. Miriam writes, how can you convince your country that delamanid is needed to be included in the regimens when WHO is not endorsing it fully?

And I would like to hear from whoever on the panel wants to speak to that.

>> I'm not sure that delamanid should be added. I think that the benefits -- it seems to me to be a rather expensive placebo. In the way that their trial was designed. The first way we should reserve delamanid for is combination with other new drugs to form entirely new regimens. And I think the WHO agrees -- well not that they agree with me. I agree with the WHO.

>> Carole, how about you? You guys have been using delamanid in the NTB project. Do you have a different opinion than Francesca?

>> Yeah, we have been using delamanid in the NTB project. Although admittedly, we are facing the challenges that I think motivated that question where countries are not as enthusiastic about delamanid as they have been, even about bedaquiline. And I guess I would go back to what Marcus said before in that while delamanid was not the blockbuster we were hoping for, according to the Phase III trial results, I think it's more than an expensive placebo. And it also has a more favorable toxicity profile than -- or safety profile I guess than many of the drugs we currently use. And unfortunately, we don't have evidence on the benefits of substituting delamanid, say, for cycloserine or for PAS, which has now sort of fallen out of favor. But I think those are areas where there might be a much better case for integrating delamanid. There's also the issue of interactions with other drugs, particularly antiretroviral therapy and I know that's been particularly managed in places like South Africa with bedaquiline. But that is another

area where delamanid may offer some benefits in ease of delivery of treatment.

>> Marcus, do you want to add anything?

>> Yes. I mean, my view is that -- you know, I don't think we can justify including delamanid as part of any standard treatment regimen at this point. But if someone has hard-to-treat NeXT TB or preNeXT TB, I would want the physician to have the option of using it.

>> Thank you. So we're coming up on the end of our time. Thank you so much to all of the audience and to our brilliant panelists. We're going to end with one last question from Dalene Von Delft. I think it's a great one.

She says that the conversation was very interesting but in keeping with Mandy's advice to keep it simple and I'll just add in keeping with the title of the webinar, now what? So maybe if each of the speakers can just say what you think needs to happen next either with national guidance or with global guidance or in the clinical trial spheres, what do you want to see happen next?

Marcus, do you want to take the first stab?

>> Yes, I think what I would like to see NeXT as is an end to the situation where we allow people to go deaf because they are poor. And that's basically what it is. We let poor people take drugs we wouldn't take. And I think our governments and the WHO in particular have to take responsibility for this. And fix it. Thanks.

>> Mandy, do you have any thoughts on what should happen next?

>> Yeah, I think that there should be a lot of focus on the high-level medium that's going to be coming up hopefully in September 2018 and trying to make sure that we have both global and country-level targets for TB diagnosis treatment and prevention. But also for R&D investment. And that's something we should engage our UN missions and policymakers on.

>> Great. Francesca, what now? Oh, I think we may have lost Francesca. Okay, Carole?

>> All right. I would concur heartily with both Marcus and Mandy. And I would add that these targets and -- these targets need to be aspirational. And one of the levers that I was referring to and that I think needs to be applied more aggressively to increase access and to find solutions is that of aspirational guidelines, as well. I do not believe that guidelines should be written to what countries can do today. Guidelines should be written to what is the best -- what is the best intervention, according to the best evidence we have. And countries should be supported and encouraged and pushed to move toward that, not to just accept the current standard and have guidelines reflect what countries can do today.

>> Thank you. Well, we're going to wrap up the webinar. We will make the handouts as well as the recording of the presentations and the presentations themselves available --

(Background noise.)

>> Probably in the next couple of days. I'm sorry we didn't get to answer everybody's questions. But I have them. So I will send an email to you and to the presenters to answer the questions that we didn't get to today.

Thank you, everybody, for participating. Thank you so much, again, to the panelists. And I hope everybody has a good day or evening, depending where you are. Thank you.