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Q1 With your extensive background in infectious diseases, particularly tuberculosis (TB), what drew you to focus on TB in adults and pediatric patients?

My mom was a nurse; so, when I was about 3 years old, I decided I was going to be a nurse just like her. I think she sensed that I was a little bit hardheaded and not good at taking orders. So, she asked me why I didn't want to be a doctor. From then on, I wanted to grow up to be a pediatrician. That was my life's goal. However, the first year I applied I did not get in. The second year that I applied, I got in on Thursday and school started on the next Monday. In my first year, I met Terry Satterwhite, who I still keep in touch with. He gave the TB lectures. Micro just kind of caught me; there's a bug, and they are extraordinary, they're smart, and they are the enemy trying to kill my patient. They are a formidable foe.

We had a lot of basic science professors, and they were pulling me to the field, but Dr Satterwhite gave more clinical talks as he was an infectious disease doctor. It just sucked me in. I loved pediatrics, it was what I wanted to do but older patients can have 40 years of drinking, smoking, and chicken fried steak in themselves, and being able to pull them out and have them feel better than they've ever felt is very gratifying. It sounds funny, but as a pediatrician, I don't like sick kids. I really like to make sure that, if they're sick, we're getting them back to right as quickly as possible. Once I pulled it all together, it was TB in adults and children, just the whole spectrum, from the womb to the tomb.

That's the backstory, but it's always in the persistence. I'd tell young folk: 'Don't ever let somebody tell you that you can't do something. You tell them what you can't do. They're not you. They don't know you like you know you. So, hang in there.'

Q2 Could you share some of the most significant findings from your work on TB, and their potential impact on TB treatment and prevention?

Understanding the stigma patients go through, and really walking with them, is crucial. We have set up a directly observed therapy (DOT) to make sure that there is somebody watching them take their meds. For me, it's making sure that they're okay and that the medications go in and there's no toxicity, and that I know about any problems they experience on the day that it happens. So, it's about getting them to a point where they understand that we're taking care of them, that we're less about dictating over them, and more so about making sure that they're okay, and walking the journey with them the entire way.

We've met patients in parking lots. My favorite story was about a gentleman who was at his work site every day. He would go around the corner to the fast-food place and get his lunch. So, the DOT worker would just meet him in the parking lot, and he would pop in the car,

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take his meds, make sure his toxicity screens were all negative, and then he would run inside, get his lunch, and go back to work as usual.

We're trying to meet people where they are, getting them more regular with their meds. We have people with substance use problems, and I tell them, I'm not here to judge you, I'm just here to make you better. It's about the patient.

From a clinical standpoint, the thing that we've been able to impact is patients who are newly diagnosed with HIV, who have not really been consistent with their meds. We offer for them to take their HIV meds when the DOT worker comes, and from this we've been able to help them see consistency with their meds, and they feel better. I remind them: 'You've been every day with your HIV meds. Look how much weight you've gained. Look how well you're doing. Look how good you feel. Don't give that back. Keep taking that med.'

With patients who are diabetic, it's about helping them with their diet. Every month, we have one little lesson about diabetic diets and about the medication, working with their physicians. So, when we step away from the TB, we want to leave them with well controlled diabetes. I think being able clinically to step in is something that we give to the patient.

I would say that from the research standpoint, we are one of the few sites of the Tuberculosis Trials Consortium (TBTC) that is enrolling adolescents. Children often get left out. We just assume that if it works in adults, it's going to work well in children. But adolescents are not adults. They have different concerns, and if you belittle their concerns, it just does harm, and it doesn't help them get to where they need to be. They don't want to take the meds. They don't want to be different.

I had a 9-year-old child who told me that they would call him to take his meds, and because he sat in the front of the room he would have to walk all the way past his peers. He felt like everybody was looking at him leaving the room, and then again when he'd come back in. So, we called the school nurse and aligned his schedule with lunch. This meant he could line up toward the back, and she would just swoop out, snatch him up, give him his meds, and launch him back into the cafeteria. The kids were so busy that they didn't even notice that he was gone.

I would say that being able to have an impact on people at one of the worst times of their lives is so important. From a research standpoint, being able to look at gearing the studies toward our adolescents, and then campaigning for studies involving younger children, and then, in the future, women who are pregnant.

Q3 You've participated in clinical studies focusing on treatment-shortening regimens for latent TB infection. How close are we to making these shorter regimens standard practice, and what challenges remain?

We're seeing impact. We were one of the sites that studied 3HP, we looked at the 3-month rifapentine-containing regimen. We saw it work, and that was really exciting. But next to that, we've incorporated it into our practice. Unless you have a contraindication, that's the one that we use. We're seeing completion rates like we have never seen before. We're pulling out data from 9 months of isoniazid, where we lost patient after patient to that. Then we went to 3 months of rifapentine, and we saw an improvement. But with the 3HP, it's just 12 doses, and we're seeing real impact. We're able to give that to children once a week at school. We're able to have adults come in once a week and receive their dosing. I would say that we're very close if we can keep the supply chains for the medications open. We went through a rifapentine shortage right when we got very excited after the regimen came out, and that seems to have loosened up again. Very recently, here in the USA, we also had an isoniazid shortage, and that really impacted almost everything we did. We have now been able to very aggressively incorporate that back in.

I would say that I think we're very close to the newest regimen, with the TBTC, that is shortening even further down to 6 weeks. I think it's looking good so far. From a patient tolerability standpoint, we won't know outcomes until we've had a further chance to follow. I really think that we're getting there. I always tell this story that in 9 months, you start with a single ovum, and you get a whole baby. So 9 months of isoniazid, it's a pill every single day. Nobody wants to do that for 9 months, and if you're not even sick, you don't see the benefit. It's hard.

Q4 You lecture both nationally and internationally on TB. In your view, how does the level of TB awareness and treatment approach differ between countries, and what lessons can be learned from these global differences?

In the USA, as part of public health, we always joke that we do things that nobody knows. I tell them that we're ninjas. We go in and take care of what needs to be taken care of, and we come back out without breaking any furniture, and nobody ever knows. That's great for your patients, less stigma, but it's not so great for you getting the messaging out there. When you tell people they have TB they're like: 'I heard my grandma had TB in the 50s. What is that?' Getting education in the lower incidence countries is very different. The stigma in the higher incidence countries is a problem; that's really the difference between talking in the two areas, having to remind people that it's very stigmatizing, and be careful with your words and the things that you say.

In low incidence countries, when things hit the media, everybody's first question is: 'Who is it?' That's the double-edged sword of alerting the public that things are happening, but knowing that we do not want the patient punished, in any way, for just having a disease.

Q5 What is the current prevalence of TB in low versus high incidence countries?

High incidence country is considered 20 cases of TB per 100,000 people. In the USA, we're close to three; we were down as low as 2.2 I think, COVID-19 just did a number on everybody. The world numbers dropped, but the African continent did not have that hard drop like everybody else, and the European region is still trying to recover. Here in the North American region, we're rebounding pretty well, but we're still behind. We haven't caught up the numbers that we lost to people being isolated for COVID-19 and taking our eyes off of the problem.

Q6 Your research work also extends into HIV. How do treatment challenges of HIV and TB overlap? Has your experience in HIV care informed your approach to treating tuberculosis, or vice versa?

I started off as an assistant professor, junior faculty in HIV. I was, till this day, fiercely protective of my patients, of their information. Now there are commercials for HIV medication, and people are stepping out of the shadows and are a little more vocal about being treated appropriately. That has gotten better, but there is still a lot of stigma. I learned early the importance of the ways you phrase things, who you speak to, who you know, just being careful about what you disclose. In the same way as with our TB patients, the first thing we do with an HIV clinic is set up a safe space. When the patient walks in and they have TB, we know their first name, we know their children, we have a

conversation. They know they are welcome here, and that nobody's going to judge them.

With HIV co-infected patients, the challenge is that TB medications sometimes compete with their HIV medications. We're making sure that we're working with the patient and their HIV provider so that all needs are being met. I think that's the more specific thing, but the stigma always runs in the background for both diseases. We're always trying to be careful if we come to screen patients at that establishment where they work.

What I learned in HIV has served me well when coming into TB. It's much easier to be very careful about disclosing people's personal information, ways that you can skirt around the answer to what the problem is, how you word your paperwork for them to be off work for a while. We're just very careful in our wording.

Treat people how you want to be treated. I think I got a lot of that from my mom. She used to tell us, when we're growing up, that nobody's better than you, and you're not better than anybody. If there's a meeting, you respect everybody, from the person who runs that meeting to the person who cleans up after. As a physician, I have a lot of patients who speak Spanish, and I always apologize that my Spanish is not as good as it could be. We have someone who speaks Spanish better than I do, but I'll kind of muddle through sometimes until my translator gets there. I'll let them know that everything is not their problem or their fault, make them feel a little bit more empowered because a lot of control is taken from you when you have TB. You have to isolate; you have to take these pills. Trying to give back some of that control to the patient, engaging them, is important. And okay, we have to take the pills, but where would you like to take them? When would you like to take them? Does it work better in the evenings? Never discount someone's side effects. No one should be expected to get up and feel sick every day.

Q7 As the world continues to grapple with emerging infectious diseases, what do you think are the key public health strategies we should focus on for controlling TB, especially in high-burden settings?

It's going to have to be education; educating people without scaring them. Educating folks on how to protect themselves, how to protect their children. Asking who the most important person is to them, and how we're going to protect them. It's about bringing it to a place where it's impactful for them. We learned a lot about COVID-19; like here in the US, you could isolate everyone, but there were people who still had to go to work. We had a disproportionate number of people who drove buses, who worked in areas where we couldn't shut down the public transit, because the people who were working in healthcare had to get to work. We had to look at how we could better protect some of the folks who make our world work. This is not unique. We have bus drivers in London. We have people who run petrol stations there. It's the same learning on how to protect those individuals all the way down to that level. But education is crucial. I really feel like the infectious diseases are going to keep coming, we're just seeing the beginnings. There'll be smaller ones, and there were smaller, less impactful waves. But this one hit us hard, and I think the waves are going to keep coming. The only way we're going to get there is by being honest in the education.

Q8 With the rising concern about multidrug-resistant TB (MDR-TB), what advancements or innovations in treatment do you find most promising?

The last free-standing hospital in the USA is here in San Antonio, and I can peep out my office window and see it. But we had people who actually lived here for 2 years taking the MDR-TB medications because they were so toxic and they were so few that you could use. We now have the BPaLM regimen (bedaquiline, pretomanid, linezolid, and moxifloxacin), and bedaquiline has been a game changer. We have a regimen that has shortened to 6 months and is almost less toxic than our drugs for susceptible disease, but we're already starting to see some resistance emerge, and that is the most frightening thing, because we don't have a backup. There are other drugs coming down the pipeline, but they're not close. We don't have one that we can switch to. So, we're back close to where we started, we're going backwards. Like I said, the bugs are smart. They wait. If you're not paying attention, they're always waiting.

I attended the Union meeting that is this month, so I'm really excited. That's usually where we get the innovations. I think there was some impetus, once we got bedaquiline and we saw how impactful that was, to try to get more options, because

we knew what was going to happen. The baseline resistance to bedaquiline is around 2.2–3%. That's low enough that we're still able to get a lot of good things done. But if you look at all of the regimens that are being studied, they're all bedaquiline based. We haven't come up with that backup drug, but now that alarm has been sounded.

I think we'll start seeing some additional drugs that are coming along. There are some that are there. There's one, TBAJ-876, that is 10 times as effective as bedaquiline, and maybe without the cardiac toxicity. There are some things that are coming, and we're hoping that they will come fast enough that we don't have patients suffering. I think the part that people always forget is that if you don't have good drugs, you're giving somebody a whole lot of medications, and the chances that they're going to have toxicity is very high and you're going to be treating them for a long time. It's not something that's going to kill you quick, it's something that's going to linger. That's always in the back of my head, some patient is suffering because we don't have anything to offer them.

I try to explain to patients that they should get treated before they become infectious. I tell them that if you break down with disease, you're not going to infect that co-worker you don't like, because you're avoiding those people. It's the people that are closest to you, that you care about the most, who are most likely to get sick. The one, I would say, blemish on what's happening right now in TB is the emerging bedaquiline resistance, because that's going to most impact the forward motions we're making. However, there's a lot of effort in treatment shortening of drug susceptible TB, shortening of drug-resistant TB. We need all the tools that we have, but it's an exciting time in TB compared to just 5 years ago. I'm very encouraged, but also very aware that the bug is very smart.

I think back to the standard RIPE regimen (rifampin, isoniazid, pyrazinamide, ethambutol) that was developed by the British Royal Army Medical Corps and only really started being clinically used in the 80s. I was in high school or middle school at that time, and I was a child when they were first doing the studies. We're only about 40 years after that. That was so impactful back then, but we've still got high numbers of TB. We put a dent in it, but we're still chugging along, we're not getting things to where they need to be. We're not getting the regimens as aggressively to the folks who need to benefit from it. Worldwide, the DOT short course had an incredible impact. I saw that with the BPaLM regimen in MDR-TB, and I think we'll still see the benefits, but our numbers are still high. That bug is not dumb.

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