# Extensively Drug-Resistant TB

*[Announcer] This program is presented by the Centers for Disease Control and Prevention.*

[Sarah Gregory] Today I'm talking with Dr. Charlotte Kvasnovsky; she's a resident in general surgery as well as a Ph.D. candidate in biostatistics. Welcome Dr. Kvasnovsky.

[Charlotte Kvasnovsky] Thank you so much for having me.

[Sarah Gregory] Ok, let's start out with some basics. What is TB and what does "drug-resistant TB" mean?

[Charlotte Kvasnovsky] Tuberculosis, commonly known as TB, is one of the most interesting diseases out there, and I say that as someone who is going into pediatric surgery which has a lot of interesting diseases. It's been a pathogen for thousands of years, it's even implicated in the deaths of mummies in Egypt. It's caused by the bacterium, *Mycobacterium tuberculosis.*

To start with the very basic: TB bacteria are spread through the air from one person to another. The TB bacteria are put into the air when a person with TB disease of the lungs or throat coughs, sings, or speaks. People nearby may breathe in these bacteria and become infected. People tend to think of TB as a disease of the lungs, but in fact it can infect any part of the body.

What's so neat about TB is how well adapted it is to living within us. While many bacteria can double their population in 20-40 minutes, the fastest TB can do so is every 20 hours. Because of this slow doubling time, it takes a long time to eliminate TB once there is an infection in place. Multiple antibiotics are needed to adequately treat tuberculosis. In fact, there are about 14 different classes of anti-TB drugs, all with different tuberculocidal or tuberculostatic effects, as well as toxicity profiles. The story of drug resistance in TB is paralleled in many other bacteria over use and improper use of antibiotics stimulates drug resistance, which makes treatment of bacterial infections more difficult.

Patients with regular, or fully drug-susceptible TB, are treated with 4 drugs, the so-called first line drugs. These are rifampin, isoniazid, pyrazinamide, and ethambutol. These drugs are safe, cheap and effective—more than 95 percent of patients can be cured with these drugs, if they take the treatment as prescribed.

The best 2 of these drugs are rifampin and isoniazid. When TB is resistant to these 2 drugs, it is called multi-drug resistant TB or MDR TB. Patients with MDR TB need to be treated with second-line drugs, which are more toxic, more expensive, and less effective. Whereas regular TB can be cured within 6 months, MDR TB is generally 24 months long. Up to 70 percent of patients with MDR TB can be cured, at least in people who don't have HIV.

MDR TB is treated with at least four second-line drugs. The 2 best drugs of these second line drugs are the fluoroquinolones, and the injectable second-line drugs, either amikacin,

capreomycin, or kanamycin. MDR TB which is also resistant to a fluoroquinolone and any second-line injectable drug, is called XDR TB, which means extensively drug resistant.

In 2014, the WHO estimated that worldwide 3.3 percent of new cases and 20 percent of previously treated cases of TB were MDR-TB. They also estimated that 480,000 people developed MDR-TB in 2014 and 190,000 people died.

[Sarah Gregory] What were you looking for when you did your study? Is XDR TB actually worse than drug-resistant TB?

[Charlotte Kvasnovsky] In 2006, I was a third year medical student at Emory University in Atlanta, Georgia. In March of that year, the first report on XDR TB was published in Morbidity and Mortality Weekly Report. By testing for resistance to second-line drugs, which was not routinely done in many places at that time, they found XDR TB in all regions tested. Rapidly, the definition of XDR TB was revised to reflect resistance to the 4 best drugs for TB as I described before.

Then in October 2006, Neel Gandhi and colleagues published a report in The Lancet on an outbreak in Tugela Ferry in South Africa, where they found 53 patients with XDR TB, 52 of whom died a median of 16 days from diagnosis. All 44 patients with XDR who were tested for HIV were co-infected.

I had been reading about HIV and TB for years, but that rapid mortality was unlike anything that had been published before. I emailed Peter Cegielski, the team leader for drug-resistant TB at the US Centers for Disease Control and Prevention, and the senior author on the Morbidity and Mortality Weekly Report publication. I was looking into work for him if that was possible.

Dr. Cegielski was running a study looking at acquired resistance during the treatment of MDR TB, the Preserving Effective TB Treatment Study, the so called PETT study. PETTS was a prospective observational study of patients with MDR TB in 9 countries, studying risk factors for, and the consequences of acquired drug resistance in the treatment of MDR TB. PETTS was a prescient study; it was proposed before XDR TB had even been described. It turned out that Peter was looking for a researcher to coordinate PETTS in South Africa, so in September 2007 I took a leave of absence from medical school to move to South Africa.

I joined the PETTS Team of South Africa at the South African Medical Research Council's TB Unit in Pretoria. The head of the TB platform was Dr Martie van der Walt. I worked in 4 provinces, but spent most of my time in Eastern Cape and KwaZulu-Natal, two of the most affected provinces. I spent a lot of time at first, at Jose Pearson Hospital in Port Elizabeth in Eastern Cape, which was where all patients in Eastern Cape with MDR TB, and then XDR TB, were hospitalized for the intensive phase of their treatment, or until they were culture negative.

I quickly met patients with XDR TB who were alive, although many of them were failing treatment. At that time the only data on XDR TB in South Africa were that patients would

rapidly die. This suggested that their treatment was essentially futile. Meanwhile, I was meeting patients with XDR TB who were walking around and living their hospital lives as normally as possible.

That was when I asked Dr. van der Walt whether I could put together a retrospective study of all patients diagnosed with and treated for XDR TB. I first got permission from Eastern Cape Province, and then later in KwaZulu-Natal Province. I wanted to find the mortality rate for the population as a whole. And then Dr. van der Walt was able to help provide guidance and some funding.

[Sarah Gregory] Tell us a little bit about your study.

[Charlotte Kvasnovsky] We analyzed data for a retrospective cohort of patients treated for extensively drug-resistant tuberculosis in 2 provinces in South Africa, Eastern Cape and KwaZulu-Natal. We compared predictors of treatment outcome in HIV-positive patients who received or had not received antiretroviral drugs with those for HIV-negative patients.

In Eastern Cape Province, all patients given a diagnosis of XDR TB by the provincial public laboratory were reported to the XDR TB treatment facility, Jose Pearson Hospital. That meant I was able to use the hospital ledger to study all patients diagnosed with XDR TB from October 2006 to January 2008. October 2006 was also the first month where drug susceptibility testing for second line drugs was available in Eastern Cape Province, and it was also the first month where additional second line drugs capreomycin and PAS were made available. So in Eastern Cape, the patients in our study were the first patients diagnosed with and treated for XDR TB.

In KwaZulu-Natal Province, new XDR TB case-patients were reported to individual clinics. The clinics then contacted the sole XDR TB treatment facility in the province, King George Hospital in Durban, to place their patient on a waiting list to initiate treatment. Our sample in KwaZulu-Natal Province included all patients who initiated XDR TB during the study period October 2006 to January 2008.

[Sarah Gregory] Is there any particular relationship between TB and HIV?

[Charlotte Kvasnovsky] TB is one of the most common opportunistic infections seen in HIV. TB is the leading cause of illness and death among people living with HIV in Africa and a major cause of death in HIV-positive people living elsewhere. In some settings, TB kills up to half of all AIDS patients.

Some 30 percent of the world's population has latent TB infection. The life-time risk of progression to active TB in normal hosts is 5-10 percent. But for the HIV-positive patients, however, the risk is 10 percent per year, much, much higher.

There are several groups of patients included in our research. We included patients who had been failing MDR TB treatment for many months, before they were finally diagnosed with XDR TB. By that time, they had very few treatment options. Other patients with advanced AIDS likely

contracted *de novo* XDR TB, which was commonly rapidly fatal. These were the same patients that were seen in the Tugela Ferry outbreak in rural KwaZulu-Natal Province from 2005-2007.

Some patients had less advanced AIDS, or already on ARVs so were able to fight their TB for longer. All of this can help explain why HIV status did not predict a favorable treatment outcome in our study, meaning the patients were already very sick when they started treatment.

[Sarah Gregory] What did you discover?

[Charlotte Kvasnovsky] We confirmed the high mortality rate for patients with XDR TB in South Africa. In our study 211 patients, or 63.9 percent of the cohort died within 2 years of follow up. Overall, 28.8 percent of patients were alive after 2 years of treatment, Interestingly, HIV status was not predictive of a favorable outcome.

Multivariate analysis showed that predictors of a favorable outcome were negative results for acid-fast bacilli at the start of treatment and a weight of more than 50 kilos. HIV-positive patients were more likely to have an unfavorable outcome. The strongest predictor of an unfavorable outcome was weight less than 50 kilos-so patients who likely already had malnutrition at treatment start.

[Sarah Gregory] Is there any way to treat people successfully with extensively drug-resistant TB? And was there any difference in successful treatment between the TB patients with and without HIV?

[Charlotte Kvasnovsky] *Emerging Infectious Diseases* accepted our article as a Synopsis, a category normally reserved for reviews of a disease or situation which provides lessons learned. The patients we describe here had just about the worst possible survival from XDR TB, because of a number of situational factors. Our initial report of 1-year outcomes for only patients treated in Eastern Cape Province, published in 2010 in the Journal of Acquired Immune Deficiency Syndromes, showed that 23.7 percent of patients died before they could even initiate treatment for XDR TB.

The DOTS-plus program started in 2000 in South Africa, treating patients with MDR TB with a standardized regimen. All patients had their initial intensive phase as inpatients, and then patients were discharged to the community to continue treatment. Most of the resources available were focused on the inpatient phase, but not on the outpatient treatment period. Many patients defaulted once they felt better, but had remaining TB infection. Some had developed acquired resistance to one or more anti-TB drugs, and eventually their disease came back. This is how XDR-TB came to be prevalent in these communities.

When XDR TB was first described in 2006, the only new drugs available in South Africa were capreomycin, which has co-resistance to amikacin and kanamycin, and PAS, para-amino salicylate. For patients failing MDR TB treatment and diagnosed with XDR TB treatment, that probably wasn’t enough to treat their TB. WHO guidelines recommend at least 4 effective drugs.

We showed only 12.7 percent of patients were on an effective treatment regimen from the start of their treatment.

It likely that given the chronicity of disease and paucity of TB treatment options available in South Africa for the study cohort, patients were unable to achieve cure by the time they were able to initiate appropriate treatment. This situation was true for patients who initiated treatment in October 2006, when XDR TB was first treated, just as it was for patients who initiated treatment more than a year later, in January 2008.

Things are somewhat better now. HIV is diagnosed earlier, and patients are initiated on ARVs earlier in their disease course, which has been shown to improve survival. In addition, there are some new drugs which may be added to the XDR TB treatment regimens, such as bedaquiline, delaminid, linezolid, and clofazamine.

Back to your initial question, even within this cohort of patients, 21 patients, 6.4 percent of the cohort, met the definition for cure and 13 patients, or 3.9 percent, met the definition for treatment completion. So overall 10 percent of patients had a favorable treatment outcome.

[Sarah Gregory] Have there been any changes in the care of HIV and TB patients in South Africa since you did this study?

[Charlotte Kvasnovsky] Yes. In addition to those I described earlier, since 2011, treatment for XDR TB has been decentralized in South Africa. As of June 2015, a total of 400 sites in South Africa were treating patients with drug-resistant tuberculosis.

There is now universal Gene Xpert testing for diagnosis. This has replaced smear microscopy, and allows for rapid detection of rifampin-resistant tuberculosis. So patients with MDR TB are being diagnosed faster. That means they are able to start the appropriate treatment faster. And because more drugs are available, including bedaquiline and the others I mentioned before, patients are more likely to be on effective treatment.

And finally, patients co-infected with TB and HIV are now rapidly started on treatment for both TB and HIV infection.

[Sarah Gregory] What do you consider the significance of your study and what do you think are the treatment needs that should still be addressed?

[Charlotte Kvasnovsky] Our study confirms that, even under suboptimal conditions, XDR tuberculosis can be cured. HIV and tuberculosis, once diagnosed, should be rapidly treated to avoid disease progression and death.

The clinical research priorities for drug resistant TB would be more effective drugs, drugs that can shorten treatment, and effective prophylaxis for drug resistant TB.

An ideal treatment regimen would not require I.V. medications, be easily tolerated with fewer side-effects, and reduce secondary cases of MDR TB.

[Sarah Gregory] Thank you, Dr. Kvasnovsky, for taking the time to talk to with me. Listeners can read the entire September 2016 synopsis, Treatment Outcomes for Patients with Extensively Drug-Resistant Tuberculosis, KwaZulu-Natal and Eastern Cape Provinces, South Africa, online at cdc.gov/eid.

I'm Sarah Gregory for Emerging Infectious Diseases.

*[Announcer] For the most accurate health information, visit www.cdc.gov or call 1-800-CDC-INFO*