Dr Vivian Cox is an infectious diseases specialist with a focus on drug-resistant tuberculosis (DR-TB). Currently, Dr Cox is the sub-Principal Investigator for the endTB clinical trial in South Africa; an Honorary Research Associate at the University of Cape Town, South Africa; Chair of the DR-TB Scale Up Treatment Action Team (DR-TB STAT); and an MDR-TB Clinical Consultant for USAID/Stop TB Partnership. She is a co-author of over 31 HIV and DR-TB publications and has 9 years of experience with new and re-purposed drugs for DR-TB treatment. From 2011 to 2016, Dr Cox was the medical manager of Médecins Sans Frontières HIV/DR-TB project in Cape Town, South Africa.

As the Chair of the Drug Resistant Tuberculosis Scale Up Treatment Action Team (DR-TB STAT) within the Stop TB Partnership, tell us about the challenges of drug-resistant TB treatment that the world is currently facing?

The challenges with the management of drug-resistant tuberculosis (DR-TB) are rapidly evolving. Up until recently, we relied on insensitive and slow tests to accurately diagnose DR-TB, and we had to use several fairly toxic medications to construct an effective treatment regimen. We also had to treat people diagnosed with DR-TB for very long periods of time – up to 20–24 months of daily medication. Treatment outcomes monitored by the World Health Organization (WHO) weren’t changing despite supportive strategies to improve the chances of successful treatment, which remained around 50 percent for years. It was difficult and frustrating for people suffering from DR-TB, the doctors that treat them, and national TB programmes.

Thanks to research and policy changes, we now have increasing access to more rapid testing for TB and drug resistance, as well as new and re-purposed drugs for DR-TB treatment. These drugs are proving themselves – both through observational cohort studies and clinical trials – to be much safer and much more effective than conventional drugs, such as the aminoglycoside antibiotics, that we used in the past. In addition to causing deafness, kidney injury, and electrolyte disturbances, this class of medicine had to be delivered through painful intramuscular injection. In contrast, newer drugs such as bedaquiline, delamanid, and most recently, pretomanid, are all oral tablets with an improved safety profile. Each of these drugs have been approved by regulatory agencies, either the U.S. Food and Drug Administration or the European Medicines Agency. Bedaquiline and delamanid are also recommended by WHO, with bedaquiline carrying a strong recommendation for use in all patients diagnosed with DR-TB when possible.

One of the top priority challenges we face now is ensuring that all people who need DR-TB treatment have access to the best diagnostic and treatment strategies that we can provide for them. Despite WHO recommendations for rapid TB diagnostics such as the GeneXpert test and oral medications such as bedaquiline and delamanid, there are large percentages of people that are not diagnosed with DR-TB due to outdated...
diagnostic tools such as smear microscopy, and that are not treated with the most effective drugs we have, such as bedaquiline and the re-purposed antibiotic linezolid. National TB programmes, as well as implementation partners, should strive to ensure WHO policy recommendations are rapidly adopted at country level for more people with DR-TB so that they benefit from these innovations in diagnosis and treatment.

It is an exciting time in the field DR-TB, since treatment outcomes are steadily improving in settings where newer drugs are being used; for instance, data from the endTB prospective observational study presented at the European Respiratory Society Congress in October showed 77% favorable treatment outcomes, and data published from South Africa's treatment programme showed a threefold reduction in mortality for people with extensively drug-resistant TB when bedaquiline-based regimens were used.1

What instruments are potentially able to speed up progress in introducing new TB drugs within national tuberculosis programmes?

The first responsibility for ensuring access to priority drugs for DR-TB treatment – including bedaquiline, linezolid, and likely in the near future, pretomanid – comes from strong leadership in various health ministries to support national TB treatment programmes with the resources they need, including domestic funding for commodities, supply chain management, or drug importation. Additionally, international partners that support DR-TB treatment implementation should work with countries to reduce barriers to newer drug use, including rapid revision of national guidelines, trainings for DR-TB clinicians, conducting operational research, and monitoring the safety of treatment regimens. Price reductions for DR-TB diagnostics and several of the priority DR-TB drugs would improve the ability of national programmes to procure the volumes needed for coverage.

How can operational research contribute to the implementation of new TB drug regimens? What TB research projects are needed to support it?

Operational research (OR) can be very valuable in its contribution to the evidence base for DR-TB management, especially when it includes high quality data collection and analysis. OR gives us important insight on how innovation, such as newer drugs, regimens, and diagnostics, perform when they are used in routine programmatic settings. This “real world evidence” often provides a more realistic picture than clinical trials, where drugs are studied in a more controlled environment.

Additionally, OR also has the potential – if it is done in a safe and ethical way – to give us information on patient populations that are often not included in clinical trials. OR can include patient populations that we know less about, such as HIV co-infected individuals or pregnant women; we often have less data to inform our treatment decisions in these groups. OR can provide information both for national TB programmes to evaluate their own treatment outcomes, as well as contribute to the body of evidence evaluated routinely by the WHO when updating their guideline recommendations. Lastly, OR provides the opportunity to strengthen data collection processes at country level.

You are a sub-principal investigator for the endTB Clinical Trial Site of Médecins Sans Frontières: what research projects for DR-TB are in the pipeline? Why are they important?

Clinical trials, because of the way they are conducted, often provide us with the highest quality evidence on diagnostics and drugs for optimal DR-TB management. There are several ongoing trials that will provide important information in the next several years not only on individual drugs, but on treatment regimens. One such trial is the endTB trial, which is a randomized control trial evaluating different combinations of drugs in completely oral treatment regimens (meaning that there’s no injection involved). They use the newer and re-purposed DR-TB drugs that have been approved by the WHO, including delamanid, bedaquiline, and linezolid and the regimens in each of the investigational arms last for nine months. Thus, not only will the trial demonstrate how we can best combine our highest priority drugs into effective regimens, but also if we can safely reduce the length of treatment. There are other clinical trials, such as TB-PRACTECAL, ZeNIX, BEAT-TB, and SimpliciTB, that will also provide answers on the efficacy and safety of different drug combinations and drug dosing strategies.

To what extent should civil society be engaged in TB research? What is the state of the art currently, and what should be done in future?

It is essential that civil society be engaged in TB research as early as possible in the drug development pipeline. It is

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the voice of the TB community, and as such, civil society can provide important inputs on patient perspectives. They are keenly aware of the human rights aspect of DR-TB – including the right to benefit from scientific progress – and hold us all responsible for research and development that best addresses the highest priority gaps in our knowledge of DR-TB treatment. Lastly, civil society plays a pivotal role in monitoring and advocating for increased, not stagnant, donor funding for ongoing research.

At the national level, what mechanisms should civil society apply to drive or support research uptake by national TB programmes and other relevant stakeholders?

A model that I’ve seen, and which works well, is used by the Global TB Caucus, and its dozens of civil society organizations from around the world. This model, when replicated at the national level, serves to bring together a diversity of stakeholders to identify and solve the particular challenges that are present in their own countries. Civil society promotes engagement with communities and higher risk groups (such as people living with HIV), assists with reducing the stigma associated with DR-TB, and supports community-based, patient-centered treatment strategies.

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