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IMPROVED DRUG REGIMENS FOR TB TO CUT TREATMENT TIME

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A campaign poster for a TB awareness program.

This November, at The Union World Conference on Lung Health 2023, there was much optimism, as it seemed that there were finally tools available to fast track work on multiple aspects of TB control. Four, new improved drug regimens that could cut treatment time for drug resistant tuberculosis by up to two thirds, were the primary source of this optimism.

For nearly five decades, few advances have been rolled out in TB care. While TB does not yet have a viable vaccine that can render prevention possible, news of possible treatments that work, and specifically address the elephant in the room in TB care- duration of treatment- naturally gets spirits up. It is the long duration of treatment, and subsequent drug toxicity, that leads to patients being unable to tolerate the drugs, and also non compliance with treatment schedules. This ultimately leads to drug resistant TB.

Echoing this optimism, Madhukar Pai, Global Health Associate Director, McGill International TB Centre, McGill University, Canada, said: “To me, the biggest progress in the recent past is the development of shorter regimens for all forms of TB, especially the 6 month all-oral treatments for drug-resistant TB. It is critical that all countries, especially India, scale up these 6 month shorter regimens for DR-TB.”

The reason is clear: treatment regimens are hard. For MDR TB, patients might require up to 14,000 pills. The problem is huge in terms of number of people affected too: MDR-TB affects half a million people each year.

On the opening day of the Union World Conference, three regimens were presented, as having achieved favourable outcomes in between 85-90% of participants for treatment of multidrug-resistant tuberculosis or rifampicin-resistant tuberculosis (MDR/RR-TB). Research led by Médecins Sans Frontières, Partners in Health, and Interactive Research and Development, found that a further fourth regimen showed a strong treatment response at 85.6% and represented an alternative for people who cannot tolerate bedaquiline or linezolid.

According to the Conference website, these drug regimens for MDR/RR-TB “represent similar efficacy and safety to conventional treatments, but have reduced treatment time by up to two-thirds.” Many living with TB face treatments that last up to 24 months, and 14,000 pills. Such

regimens can be ineffective, with only 59% treatment success in 2018, and can often cause terrible side effects. Some patients even have to endure months of painful, daily injections.

Over 750 participants from 11 sites, 7 countries, and 4 continents were involved in the study , funded by Unitaid, on tackling MDR/RR-TB. The trial showed how combining antibiotics in new ways could treat this form of the disease more effectively than ever before, offering much-needed hope.

Carole Mitnick, Professor of Global Health and Social Medicine at Harvard Medical School and Partners in Health Director of Research for the endTB project, said: “We stand on the cusp of a significant breakthrough in the battle against MDR, a disease that disproportionately affects impoverished populations around the globe. Our results offer hope to those in dire need and underscore the urgency of continued research and innovation—and accountability of private companies that receive public funds—to address diseases that too often strike the most vulnerable among us.”

The researchers’ findings are a significant step and could address issues around access to and affordability of quality TB care, experts agree.

Soumya Swaminathan, former Chief Scientist, World Health Organisation, and current chairperson of the MS Swaminathan Foundation, says: “It is really encouraging, especially for the treatment of MDR TB where the outcomes are currently very poor – there are efficacy and compliance issues, and some severe side effects for long treatment. When you look at results of the short regimen studies (presented at Paris), it nearly seems like a miracle. If we are able to achieve an 85 % and above cure rate, it would indeed be a real boon for patients with MDR TB.”

Did fast tracking of pharma research and development have an impact on hastening the pace of TB drug development? “No. The trials were planned well before the pandemic. It was very tough, getting funding, and approvals from different countries. But over the last decade or so, a lot of work behind the scenes has been put into advancing the R&D in TB agenda, including by the WHO, Stop TB Partnership, the Treatment Action Group (TAG). The TB alliance has also been doing a significant amount of work,” she explains.

The United Nations High-Level Meeting on TB in 2018 set the target of US$2 billion per annum for R&D. In December last year, TAG and Stop TB Partnership announced that for the first time in history, funding for TB R&D hit a billion dollars worldwide in 2021. “This marked a significant milestone that nonetheless falls significantly short of what’s needed to stay on track to end TB,” according to their report. After years of chronic underinvestment and devastating disruptions caused by COVID-19, the Stop TB Partnership’s *Global Plan to End TB, 2023–2030* estimates the funding need for TB R&D to have gone up to US$5 billion per annum.

The bulk of this funding has come primarily from the government and philanthropic contributions, Dr. Soumya adds. “It is combined efforts over a decade that have resulted in these advances. But the pace is yet too slow, if you take into account the number of people affected by, and dying of TB. A stronger commitment to come up with a vaccine is needed, globally.”

She emphasises that the attack on TB should be on multiple fronts, in order to be able to eliminate the disease. Another big gap exists in the area of case detection in reality. While TB diagnostics have been technically ushered into the modern age with sensitive molecular tests, and AI assisted conventional tests, in India, sputum smear microscopy continues to be the deployed the most, though some State governments have made headway with advanced devices to diagnose TB. The WHO says over-reliance on direct sputum smear microscopy is inherently associated with a relatively high proportion of pulmonary TB cases that are clinically

diagnosed, as opposed to bacteriologically confirmed. Sputum smear microscopy reportedly has about 50% sensitivity, and therefore contributes to the huge burden of missed cases in the country. It is also not equipped to diagnose cases of drug-resistant TB.

The world, today, has X-rays with AI assistance to flag abnormalities, AI-assisted cough diagnosis, new advances in the molecular detection of TB, multiple products built on the faster nucleic acid amplification test (NAAT) and whole-genome sequencing.

In a recent paper published in the *Indian journal of Medical Research*, Dr. Soumya and Dr. Pai wrote in the article '*India is well placed to scale innovations in tuberculosis diagnostics'*: Several molecular tests are now endorsed by the WHO, including Xpert MTB/RIF Ultra (Cepheid Inc., USA), TrueNAT MTB and TrueNAT MTB-RIF Dx (Molbio Diagnostics, India), loop-mediated amplification (LAMP-TB), assay line probe assays and centralized assays. Some are low-complexity tests, while others are moderate-to-high-complexity assays.

It is crucial to deploy all these tools in order to find every person who has the infection, Dr. Soumya says.

Again, at the Union World Conference on Lung Health Tony Hu, Professor at Tulane University, spoke of how rapid portable, battery-operated tests could be a new tool for point-of-care TB testing requiring minimal equipment and user expertise. Point-of-care testing does not require specialised clinical or laboratory equipment, making this an invaluable tool in preventing the spread of a disease through early detection. Additionally, it has the potential to be scaled up quickly if disease hotspots are identified, allowing scientists to respond rapidly to TB outbreaks, Dr. Hu explained. Also on display was an interesting experiment: researchers from Tanzania, Belgium, Mozambique, and Ethiopia presented an analysis into rats that could sniff out TB.

Dr. Pai, who is also a grand advocate for newer diagnostic tools adds: "Another big takeaway is the growing acceptance that we must phase out old diagnostic tools like smear microscopy and replace them with rapid molecular tests. This is essential to narrow the big diagnostic gap."

(ramya.kannan@thehindu.co.in)

TrueNat machines at a PHC in Ponda, Goa. Goa has embraced upfront molecular diagnostic testing for TB, even at the PHC level. Doctors in Goa claim their testing rate has improved since then.

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