NEWS

TB experts elated as new drug cocktail cuts therapy and reduces side effects

Drug-resistant TB remains a public health threat in SA with a cure rate of just more than 50% for MDR and 27% for XDR

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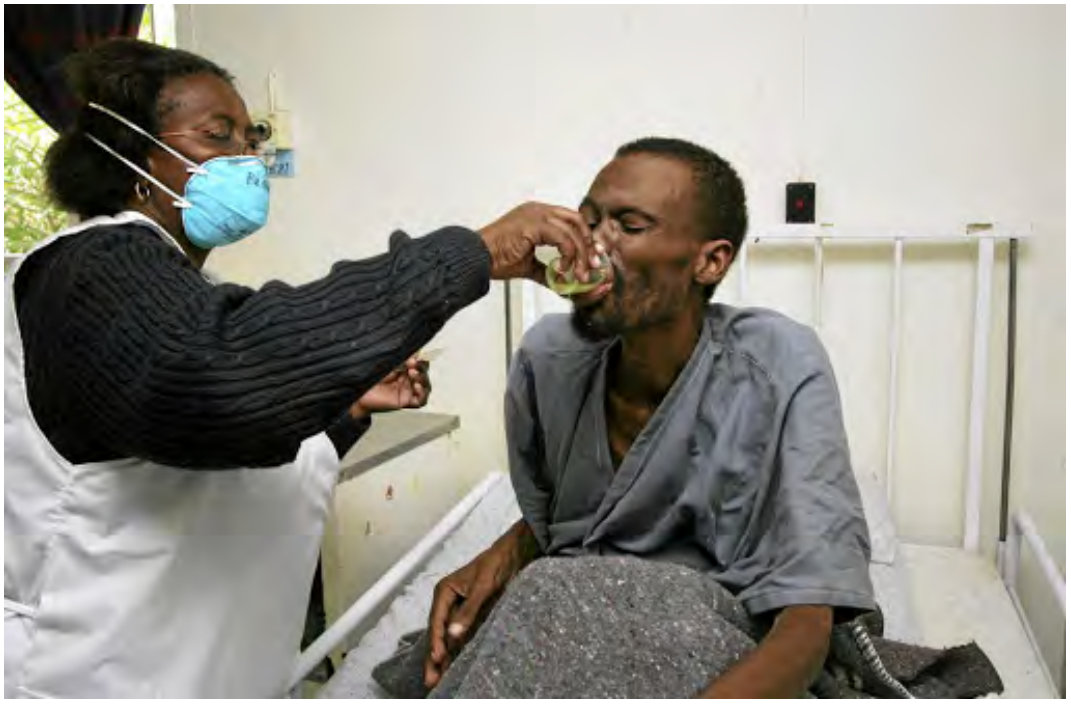


A patient with extensive drug-resistant tuberculosis at Jose Pearson Hospital in Gqeberha, Eastern Cape. New evidence that shows less side-effects to drug-resistant TB treatment has been welcomed by experts.
Image: *CHRIS FREY*

Apart from the lengthy healing period, dreadful side effects and the burden of swallowing many pills have often been blamed for the treatment failure of those living with drug-resistant tuberculosis.

But experts have renewed hope after new data showed that not only can this form of TB be treated in a much shorter period using newer drugs — bedaquiline, pretomanid and linezolid (BPaL) — but side effects can drastically lessen by lowering doses without compromising treatment outcomes.

On Wednesday, the findings of the ZeNix study conducted in SA, which evaluated whether the efficacy of a three-drug regimen can be maintained while reducing toxicity through a lower dose and shorter duration of linezolid, were published in the New England Journal of Medicine, along with new evidence from the US that showed a similar result.

> **While the results are very encouraging, it highlights that efficacious but less toxic drugs are required.**
>
> *- Keertan Dheda, UCT professor of pulmonology*

A letter from the US Centres for Disease Control (CDC) and Southeastern National TB centre was also published in the issue, describing the treatment experience of the first 20 patients on BPaL in the US. The letter indicated that by 12 months after initiation, 19 (95%) patients had completed therapy with no treatment failures, recurrences or deaths.

“The results of this study reaffirm the potential of this regimen. It’s encouraging to confirm that we can continue to offer patients a high likelihood of rapid cure while improving the treatment experience,” said Francesca Conradie, principal investigator for the ZeNix clinical trial and SA’s clinical access programme for the regimen.

Data from ZeNix contributed to a rapid communication from the W Health Organisation (WHO) in May, indicating new guidelines that w...

enable countries to treat virtually all patients with DR-TB with BPaL-based regimens.

A year ago preliminary findings of the study ZeNix did in SA and 10 other sites across the world by non-profit TB Alliance and Wits University, among others, revealed that efficacy of the new regimen — yet to be introduced in SA — does not decrease even when the linezolid dose is halved.

Despite its efficacy, it was its adverse effects such as peripheral neuropathy (numbness caused by nerve damage) and myelosuppression (decreased bone marrow activity) in patients that remained a concern.

Of the 181 participants enrolled in the four-arm randomised ZeNix, 36 (20%) were HIV positive. Participants who either had XDR or failed MDR were treated for six months with bedaquiline, pretomanid and varying doses and durations of linezolid, with follow-ups until the primary endpoint six months after completion of treatment.

The study sought to evaluate whether the efficacy of the BPaL regimen could be maintained while reducing a patient's exposure to linezolid and its associated side effects.

The success rate for participants receiving the highest dosage of linezolid (1200mg for six months) was 93%, while in those receiving 600mg for six months the efficacy was 91%, and 84% among those receiving 600mg of linezolid for two months. Researchers argue these findings are consistent with the 90% success rate of the BPaL regimen in an earlier trial, known as Nix TB trial.

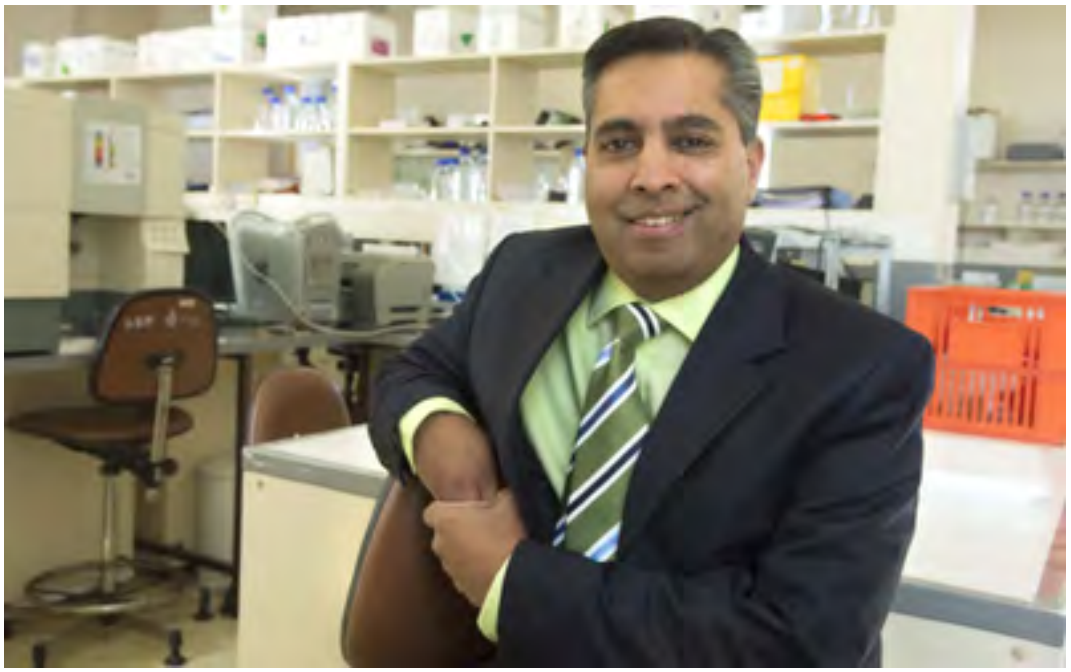
In the latest trial, peripheral neuropathy was found in at least 10% of participants. Those that received high doses of linezolid for a longer period saw an increased number of peripheral neuropathy cases. Evaluation of myelosuppression, which manifested as anaemia, found that patients exposed to linezolid for a longer period had more adverse effects than those either on a lower dose or shorter period of exposure, but these were overall much lower than in earlier research.

Local experts are encouraged by the latest result, especially for a country such as SA, where drug-resistant TB remains a public health threat with a cure rate of just more than 50% for MDR and 27% for XDR.

Public health expert and UCT professor of pulmonology Keertan Dheda described the latest findings as "very encouraging".

"After a period of several decades, we are seeing newer and improv regimens for the treatment of drug-resistant TB. This is extremely

important because the death rate with drug-resistant TB is about 30% and many are left with chronic lung disability."



Prof Keertan Dheda of the UCT Lung Institute has described the improved regimens for the treatment of drug-resistant TB as encouraging.
Image: *University of Cape Town*

He described the endorsement of the new regimen by WHO as a "major advance because it no longer uses toxic injectable drugs and the duration of treatment has now been reduced from 18 to only six months ... the same as for drug-sensitive TB".

The WHO Global Tuberculosis Report 2020 indicates that about 360,000 people in SA contracted TB in 2019. This is a 20% increase over the 2019 report that estimated 301,000 people fell ill with TB in 2018. According to the report, about 58,000 people died of TB in SA in 2019.

Dheda said the study also raised a red flag due to the side effects produced by linezolid in a significant proportion of patients. "While the results are very encouraging, it highlights that efficacious but less toxic drugs are required. Other very important measures are to reduce the overall burden of TB in the first place by reducing rates of HIV, reducing cigarette smoking, reducing poverty and overcrowding."

Mel Spigelman, president and CEO of TB Alliance, said the latest results add to the substantial evidence base for the efficacy and safety of the BPaL regimen. "It will enable care providers to further optimise use of the regimen. We will continue to innovate and fight for access until the days of lengthy and highly toxic therapies are over for every person with TB"

Health department spokesperson Foster Mohale said the new findings had been included in the department's BPaL access programme — an initiative of the Wits Health Consortium and health department to provide a new, shorter treatment regimen for people affected by highly drug-resistant forms of TB. The pilot programme has enrolled 400 people with drug-resistant TB.

Work is under way to amend the country's national guidelines for drug-resistant tuberculosis (DR-TB) to provide the new six-month, all-oral regimen as a new standard of care treatment. Mohale said the department was hoping to upscale this into the BPaL regimen before the end of the year.

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