

## TB: The tap's down a notch – but the water's polluted



South Africa (SA)'s drug-susceptible (DS) tuberculosis (TB) 'tap' may have been turned down a few notches by the sustained HIV/AIDS testing and antiretroviral therapy (ART) campaign, but a growing number of dying, drug-resistant (DR) TB sufferers are desperately awaiting the approval of drugs known to be effective.

This emerged from SA's top researchers, activists and coalface clinicians across the public and private sectors as they outlined the latest TB countermeasures for 1 500 delegates attending the 4th National TB Conference at Durban's International Convention Centre between 11 and 13 June this year. Another stark fact to emerge was that only a TB vaccine – the frustrated developers of which are now turning to direct human trials for testing – will turn off the tap of new infections and take SA off the top of the list of countries hardest hit by TB.

Bedaquiline, the most effective new TB drug to emerge globally in 40 years, has resulted in promising response to treatment in 75% of patients after 3 months of treatment in the ongoing SA compassionate use programme (almost four times the efficacy of existing locally registered drugs for extensively drug-resistant (XDR) disease). However, at the time of writing, the Medicines Control Council (MCC) had not approved it for anything other than highly controlled compassionate use. A top TB researcher and a senior national health official intimated at the conference that authorisation for more generalised bedaquiline use, and a far cheaper (and therefore more applicable) generic version of linezolid (also a highly effective combination therapy drug), was 'imminent'. Currently, treatment of DR TB consists of at least four toxic drugs (including an injectable agent), administered over 2 years. It is costly and a painful ordeal for patients, with a significant number of those who survive ending up deaf. A promising 6-month, five-drug, injection-free trial, involving both new drugs and funded by the Medical Research Council to the tune of R18 million, is underway, co-led by the University of Cape Town's pulmonology chief, Prof. Keertan Dheda.



From left, Prof. Keertan Dheda, head of pulmonology at the University of Cape Town and Groote Schuur Hospital, Dr Nazir Ismail, National Health Laboratory Service Reference Laboratory, and Dr Willem Hanekom, Director, SA TB Vaccines Initiative. Picture: Chris Bateman.

### More general use for bedaquiline 'imminent'?

Dheda believed that with about 100 South Africans currently on bedaquiline (compassionate use), MCC approval for more general application was 'imminent'. With full clinical trial data not yet available, it would 'obviously have to be used in a very responsible way'. 'How we will use it and with who' remained open questions. 'At the end of the day we'll have to put it into a regimen to trial it before we know how it works, whether it's efficacious, and how it interacts with other drugs,' he added. However, at the same time, as lives were being lost it was difficult to withhold the drug from patients who could potentially benefit. With a 'known' DR national caseload estimated at 8 000 patients last year (up from 6 500 patients treated in 2012), drug resistance in SA is now the single biggest challenge to a belatedly up-scaled and re-prioritised TB programme. DR TB stands at just below 3% of the total TB caseload, but the strains are virulent, spreading most notoriously from person to person in prisons, in crowded public transport vehicles and in and around the country's mines. DR TB now consumes nearly half the nation's TB resources, creating an unsustainable economic equation. Speaker

after speaker at the conference dispelled the myth that the ongoing DR TB spread was the result of non-adherence or treatment failure, emphasising that airborne transmission was now the major mode of spread. In non-ventilated environments, catching it is as simple as 'you breathe out and I breathe in'. Doing the basics right, such as triaging TB and HIV patients, wearing proper masks and dramatically increasing ventilation, was perhaps best illustrated by Dr Gerald Friedland, Professor of Medicine and Epidemiology and Public Health at Yale University in the USA.

### Global lessons from Tugela Ferry

Friedland catalogued the 'rise and fall' of XDR TB at Tugela Ferry, where it was first detected in 2005 by the local Church of Scotland Hospital veteran chief medical officer, Dr Tony Moll. Friedland said a dramatic correlation with extremely low infection rates was revealed by simply opening all windows and using fans in all TB wards. With ward windows closed and the mechanical ventilator off, one (room) air change per hour was recorded. With windows closed and the mechanical vent on, this rose to 15 air volume changes per

hour, while with all windows open and mixer fans on, more than 60 air changes per hour were recorded. By focusing on airborne infection control, protecting staff with N95 masks, screening for TB at all hospital entrance points and separating and fast-tracking coughing HIV patients, almost half of all anticipated DR TB cases in the hospital environment were avoided.

The proportion of DR TB to DS TB cases at Tugela Ferry (taking into account the introduction of ART) had dropped from 65% in 2005 to zero by last year. Friedland said that a whole array of community-based strategies, including early case finding, rapid diagnosis (with GeneXpert), community-based treatment and more standard household contact tracing, were 'brilliantly employed' in the Msinga district of Tugela Ferry. This had resulted in KwaZulu-Natal (KZN), with top international academic and clinical support, adopting a multipronged multidrug-resistant (MDR)/XDR TB combat protocol that has since been embraced nationally and globally. Between the time a stunned Tony Moll uncovered the first DR (XDR) TB cases (53 in a 350-bed hospital) in January 2005 and January 2008, Tugela Ferry held the world's single largest known concentration of DR TB (82% of XDR patients and 67% of MDR patients died over this period, as did nine healthcare workers). Fears that this was not simply an isolated 'outbreak' were soon confirmed when more than 60 KZN healthcare facilities were found to be affected – before public health officials discovered that it was spread across all nine provinces. Dheda described the Tugela Ferry event as 'the perfect storm'. 'You had a very susceptible group [advanced HIV patients] with a virulent TB strain in a very contained environment. At the time there were no ARVs available and no treatment for XDR TB.' Friedland – and several other epidemiologists and clinicians at the conference who showed complex graphs and bar charts of TB mutations, drug trials and regimens, and the alarming and growing prevalence of MDR TB – took pains to remind their audience constantly that the statistics were actually 'human beings with the tears removed'.

**Motsoaledi: 'No need for "emergency" – we're doing all we can'**

National health minister Dr Aaron Motsoaledi rejected urgent calls by healthcare activist groups, including the Treatment Action Campaign (TAC) and Section 27, to declare MDR TB a national health emergency



*Yale researcher Dr Gerald Friedland and Tugela Ferry's Dr Tony Moll. Picture: Chris Bateman.*

with 'war rooms' in every province, claiming that all available strategies were already being deployed.

'It's difficult for me to see the benefits of such a declaration. I believe we have at our disposal all the weapons that civil society is asking for. The question we need to ask ourselves is, are we able to implement these plans?' He and his national TB chief Dr Lindiwe Mvusi outlined a multipronged newly refined approach to countering TB in all its manifestations, including strategies to deal with populations in prisons, on public transport and in mines and detailing patient follow-up collaboration with SA's neighbouring countries. Motsoaledi committed his department to increase existing screening of mineworkers to half a million, plus another 600 000 people in the surrounding mining communities, with both populations benefiting from the resultant treatment. Having secured the signatures of his counterparts in Lesotho, Mozambique and Swaziland to actively synchronise continuity of treatment and referral of mineworkers, plus sharing software on a common database (courtesy of the Bill and Melinda Gates Foundation), the remaining dozen or so nearest countries had so far signed a 'declaration of intent'. A common treatment protocol had been developed with colour-coded, patient-friendly drug charts. The Global Fund for HIV/AIDS, TB and Malaria has allocated R500 million to the project, given that five of the countries carrying 80% of the world's TB burden are situated within the Southern African Development Community. Former Swaziland health minister Benedict Xaba is spearheading the project.

Mvusi told *Izindaba* that even if the employer mines had to send treatment to their boarded foreign workers, or patients had to travel back on a regular basis for treatment, her department would help ensure this continuity of treatment as a minimum requirement in addition to any other compensation they deserved. She said that in prisons, from March last year all newly admitted offenders (or on-trial inmates) were being screened for all medical conditions upon entry, with proper guidelines now issued. Anyone who was symptomatic was immediately isolated for at least a week, returning to their cells once started on treatment. A recent study by the mines-funded Aurum Institute found that 4% of surveyed inmates at one Gauteng prison had TB but did not know it and a quarter of inmates were also HIV-positive, skyrocketing their chances of getting TB (an up to 30-fold risk increase). Mvusi said infection control awareness education had been stepped up, including around transferrals between prisons and upon discharge, with strict referral to district hospitals and community clinics. Longer-term inmates now had to be screened twice a year and X-rayed if symptomatic. She said that while wholesale rebuilding of prisons to improve ventilation was virtually impossible, Prof. Adriano Duse, head of Clinical Microbiology and Infectious Diseases at the National Health Laboratory Service (NHLS) and the University of the Witwatersrand, would lead a Council for Scientific and Industrial Research team in conducting infection control risk assessments in prisons and 'come up with plans'. 'I just hope they can reach an accommodation between security and ventilation,' she stressed.

*With a 'known' DR national caseload estimated at 8 000 patients last year (up from 6 500 patients treated in 2012), drug resistance in SA is now the single biggest challenge to a belatedly up-scaled and re-prioritised TB programme.*

**New TB guidelines issued**

The national health department had also issued new Correctional Services guidelines on voluntary HIV counselling and testing, screening, 6-monthly CD4<sup>+</sup> testing for inmates who did not meet HIV treatment initiation requirements, and isoniazid preventive therapy for all candidates who met its strict criteria. Preliminary results from a

GeneXpert trial across all 242 prisons were already showing 'a very significant reduction in TB'. Mvusi cited the national incidence of TB in SA as standing at 1 003/100 000 people.

Meanwhile SA is seeing about 18% fewer new TB cases annually as a result of the increasing number of HIV-positive people on ARVs following the massive national counselling and testing push over the past several years. Professor Nazir Ismail, head of the National Institute of Communicable Diseases, told delegates that the drop came after year-on-year increases of TB cases peaked dramatically in 2008, before beginning a slow annual decline in lab-confirmed cases that had continued to the present. He was confident that the decline was accurate, because of the 300% increase in the number of people tested for TB since 2004.

### GeneXpert's potential limited by lack of capacity

Ismail revealed that SA was now responsible for at least half of the global GeneXpert roll-out. GeneXpert rapidly and simultaneously detects TB and rifampicin resistance, and from 2011 has replaced the slower and less accurate traditional TB tests. A recent trial comparing GeneXpert with smear microscopy had shown 83% accuracy for the former compared with 50% for the latter, GeneXpert detecting TB in most patients within 1 - 3 days (77%) v. smear microscopy which detected half the patients in the same time. Because of its speed, GeneXpert reduced culture-positive drop-out rates from 16% to 9%, a key benefit being that 'you can do it in front of the patient'. Ismail said it was 'critical' to get patients on treatment early to reduce contagion, citing an 80% person-to-person transmission rate in China. GeneXpert was highly feasible in primary care settings, did not require high-tech staff, and increased same-day result rates. Research by Dr Pren Naidoo of the Desmond Tutu TB Centre has shown that on average, MDR TB patients took 16 days to begin treatment following the receipt of their same-day GeneXpert results – strongly underscoring Ismail's warning. Since the GeneXpert roll-out, the average time between testing and treatment initiation for regular TB patients had dropped from 4 to 6 days. Patients with MDR TB now started treatment 26 days sooner than previously. Naidoo said that lab costs had doubled with GeneXpert's introduction, but this was offset in some parts of the country by increased TB diagnosis. The new technology had 'incredible potential', but on its own it could



National Department of Health TB chief Dr Lindiwe Mvusi. Picture: Chris Bateman.

never prove a panacea because of the poor-to-dysfunctional provincial health system.

### Linezolid generic possible by November

Pressurised by treatment activists, lawyers and clinicians during a patient advocacy session, Dr Yogan Pillay, Deputy Director-General: Strategic Health Programmes in the national health department, surprised many by revealing that linezolid would 'shortly be coming off patent' at a much-reduced price. He said Mvusi's department would have to make crucial and 'innovative' choices about how to use the drug to get the best possible outcomes for the most patients. 'We're not just talking specialist XDR TB hospitals here, but much broader than that.'

Pressed on bedaquiline, he said that because of the strict MCC access rules, sufficient safety data would have to be garnered 'before we can say we can use this outside the clinical access programme'. He speculated that this 'might happen around November', before pleading with journalists to source this information from the MCC itself. 'I've been on the [MCC] registrar's "case" trying to ensure they pass the review of the [generic companies'] dossier on linezolid on the same basis as they approved off-label use of bedaquiline, and to get permission to have it as part of the clinical access programme.' TAC veteran Mark Heywood asked whether provincial health leadership was competent enough to carry out progressive national health policies under Motsoaledi. He said that the call for a national health emergency came

in the context of 'thousands and thousands of preventable deaths', including hundreds of healthcare workers, as a result of poor infection control.

### MDR crisis: 'Don't forget to close the DS TB tap' – Pillay

Pillay said that with new, lifesaving back-up drugs in the offing and with GeneXpert offering new hope, 'before we even deal with MDR in the way people suggest that we should, we need to deal with regular TB in ways that close the tap. We're clearly challenged with MDR and XDR, but we need to close the tap of DS TB. We've been able to show cure rates and treatment success rates going up [for DS TB] – clearly not fast enough, because we still have about 6% default rates.' He cited government decisiveness on DS TB, with Motsoaledi accelerating decentralised TB diagnostics and treatment to 2 500 sites in all 52 health districts. The target was to get another 3 000 MDR patients onto treatment over the next 2 years, plus adapt the highly successful nurse-initiated ARV management and treatment (NIMART) to a TB model, thus extending care to thousands more patients via task shifting from scarce doctors.

### Vaccines – a radical rethink required

Dr Willem Hanekom, director of the South African TB Vaccines Initiative, currently on sabbatical as deputy director in Global Health (leading the Bill and Melinda Gates Foundation's TB vaccine programme), said a 'complete rethink' was required on TB vaccines. The 15 TB vaccine candidates currently in clinical trials were all developed in 'virtually the same way', stimulating the same kind of immunity. All were tested on animals, and 'we're not sure the results they show will be successful, ultimately'. While animal testing would continue, the new strategy would be to conduct human testing 'as early as possible, with safety paramount'. Using human data to guide scientists was now the preferred path. Many hurdles, including regulatory approval, how to make new candidate vaccines and conducting numerous small studies, had yet to be overcome. The bottom line was that 'a radical rethink is required to move ahead', he added.

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