The results imply that stratifying patients with ARDS based on mechanistic endotypes could enable better alignment between patients and potential therapies, and this parallels recent observations in other critically ill patient populations. For example, leukocyte transcriptomics has shown that a subset of patients with sepsis show an immunosuppressed phenotype (ie, features of endotoxin tolerance, T-cell exhaustion, and human leukocyte antigen class II downregulation),[11,12] supporting previous epidemiological observations that suggest genetic heritability of mortality risk in the setting of infection.[13] This underlying immune heterogeneity could partly explain why numerous immunomodulatory studies have failed to improve outcomes in unselected patients with sepsis.[4] Similarly, mechanistic disease endotypes probably exist in other critically ill patients, including those with cardiogenic shock,[14] and features of such endotypes could overlap between critical illness syndromes.

The next steps in translating these findings include identifying reliable, clinically-accessible biomarkers of disease endotypes; understanding whether modifiable or genetic factors determine endotypes; further whether endotype-stratified approaches could improve outcomes in failed therapeutic strategies;[15] and eventually incorporating disease endotypes for prognostic or predictive enrichment in clinical trial designs. Furthermore, considering conserved, homologous responses to acute illness across diverse critical care syndromes might one day open avenues for critical care basket trials, targeting common molecular responses across various critical illness states. The study by Calfee and colleagues[7] represents a crucial step towards the next frontier of acute care.

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Bedaquiline use in South Africa reveals a lifesaving policy in action

"May your choices reflect your hopes, not your fears."
Nelson Mandela, 1994

Referred to as a "ticking time bomb", "Ebola with wings," and "killer TB",[1] rifampicin-resistant tuberculosis—with its airborne transmission and treatment success rate of around 50%—is a terrifying disease.[2] With standard treatment for rifampicin-resistant tuberculosis lasting between 9 and

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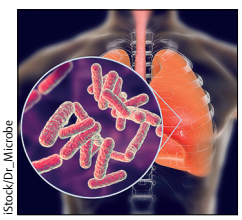
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24 months, and comprising several highly toxic drugs—including the painful daily injectible agents kanamycin, capreomycin, and amikacin—that can result in deafness, it is understandable that some consider this diagnosis to be a fate worse than death.[3]

Nevertheless, after a lull in drug development lasting almost half a century, in 2012 bedaquiline, a novel agent active against *Mycobacterium tuberculosis*, was approved for treatment of rifampicin-resistant tuberculosis by the US Food and Drug Administration.[4] Disappointingly, uptake of this exciting new drug has been sluggish. Some of the slow uptake can be blamed on results from a phase 2b trial, which although showing statistically significant and improved overall outcomes in people who received bedaquiline compared with placebo, also showed a higher mortality rate in the bedaquiline arm.[5] Even though the number of deaths in both groups was small and none of the deaths were attributable to bedaquiline, because this drug is known to cause QTc prolongation, policy makers, programmes, and providers have been fearful of its use. For example, both the 2013 and 2017 WHO interim guidance on bedaquiline recommend the drug only be used in situations where people with rifampicin-resistant tuberculosis have no other treatment options, and only if the country or programme using the drug meet strict criteria.[6] Conservative recommendations for use, coupled with the high price of bedaquiline and a pervasive notion that the drug needs to be protected for future generations, have all contributed to the inadequate roll out of this medication.[7]

However, in South Africa the devastation of the rifampicin-resistant tuberculosis epidemic has been hard to ignore. High rates of second-line drug resistance coupled with an overwhelming HIV co-pandemic mean that a person diagnosed with rifampicin-resistant tuberculosis in South Africa has almost a one in three chance of dying while on treatment[8]—a poorer prognosis than for many forms of cancer. Rather than sweep this crisis under the rug, the South African National Department of Health has been determined to face the escalating problem head on.

Under the leadership of the South African National Tuberculosis Program, and with the support of non-governmental organisations and policy makers at the local and provincial level, clinical trial sites that had participated in early bedaquiline studies joined forces with front-line clinicians and began using bedaquiline under monitored conditions for specific indications through the Bedaquiline Clinical Access Program.[9] Once bedaquiline was registered in South Africa in 2014, use was scaled up nationally as an additional drug to strengthen treatment for people with rifampicin-resistant tuberculosis with more extensive resistance, and for drug substitution where there was toxicity or high risk of toxicity from the medications in the standard rifampicin-resistant treatment regimen. Bedaquiline use increased dramatically in central tuberculosis hospitals and primary health-care clinics and in both urban and rural settings. Given the high rates of HIV co-infection in patients with rifampicin-resistant tuberculosis in South Africa, the National Tuberculosis Program decided there was an ethical obligation to provide equal access to bedaquiline for people with HIV, as well as for other groups that could benefit (such as adolescents and pregnant women), despite global guidance cautioning against use in these populations.

The results of these collective actions, presented in *The Lancet Respiratory Medicine* by Kathryn Schnippel and colleagues,[10] show how prescient and impactful South Africa's decisions were. This Article is a retrospective cohort review comparing thousands of people diagnosed with rifampicin-resistant tuberculosis in South Africa between 2014 and 2016 who received bedquiline-based regimens with those who did not. The study found that people with rifampicin-resistant tuberculosis who were treated with bedaquiline were more likely to survive—even though they were often sicker and had higher levels of drug resistance—compared with those who received standard tuberculosis treatment regimens (hazard ratio 0·35, 95% CI 0·28–0·46). Those who received bedaquiline had lower mortality overall (12·6%, compared with 24·8% in the non-bedaquiline group).[9]

Although there are limitations to this study due to its retrospective nature, a potential survival bias, and the fact that people receiving bedaquiline might have been more closely monitored, the results are striking and suggest that under field conditions, use of bedaquiline within a rifampicin-resistant tuberculosis treatment regimen might be associated with a lower risk of death. Although it will be important to see these results confirmed with phase 3 trials and additional cohort studies, the life-saving work done in South Africa should lead to broader global recommendations for use of bedaquiline in the

routine treatment of rifampicin-resistant tuberculosis. The recent decision by the South African National Tuberculosis Program to offer bedaquiline to most people diagnosed with rifampicin-resistant tuberculosis in place of injectable drugs rings as a call to action.

South Africa's leadership in rolling out novel tuberculosis therapeutics should stand as an inspiration for all of us who aim to end tuberculosis, which will only be possible if innovation is embraced. In fact, of the 16 639 patients started on bedaquiline globally as of April 1, 2018, most of them (10 429; 62·7%) live in South Africa.[11] Thus, although the WHO End TB strategy speaks about bold policies for tuberculosis elimination and all eyes are trained on New York for the UN's first high-level meeting on tuberculosis in September, 2018, those wishing to move beyond political promises and to successful public health action should look to South Africa. There, in the context of one of the most devastating rifampicin-resistant tuberculosis epidemics in the world, is an exemplary model of how lives can be saved when person-centred policies are coupled with brave acts and visionary leadership. South Africa's approach to the use of bedaquiline should be emulated in other countries; the decreased mortality observed among people receiving bedaquiline through South Africa's National Tuberculosis Program provides hope that it is possible not only to talk about a tuberculosis-free world, but to actually create one.

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That's a WRAP: laparoscopic anti-reflux surgery for idiopathic pulmonary fibrosis

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The highly anticipated results of WRAP-IPF are in—Nissen fundoplication appears to be safe and well tolerated in patients with idiopathic pulmonary fibrosis (IPF) and abnormal gastro-oesophageal reflux (GER).[1] The primary endpoint of slowing lung function decline was not met in this underpowered phase 2 trial by Ganesh Raghu and colleagues, but the numerical trends are promising enough that anti-reflux therapy warrants further study as a treatment for IPF.

This US National Institutes of Health-funded trial was borne out of the debate surrounding the role of GER in the pathogenesis and progression of IPF, and conflicting findings from retrospective studies of antacid therapies on survival and disease progression.[2–4] Prior studies[5] of oral antacids have had important limitations, yet the 2011 international guideline on treatment for IPF conditionally recommended antacid therapy for all patients, a point that is steeped in controversy.[6,7] Although antacids reduce the acidity of gastric contents, they do not eliminate reflux or non-acid GER, both of which are potentially pathogenic. Laparoscopic anti-reflux surgery tightens the lower oesophageal sphincter to prevent gastric reflux into the oesophagus and upper airway, leading to reduced risk of microaspiration and its potential sequelae. Surgical guidelines suggest that, in the presence of documented reflux, surgical intervention should be considered in patients for whom medical management was not effective, have a preference for definitive surgical