

# HATiP

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# Towards more compassionate care for people with drug-resistant TB

By Theo Smart

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*"Our response to the emergence of drug-resistant TB is profoundly ethical as it raises issues of how justice and human rights are realized in our collective response to a disease. It also underscores how the global community responds to its most disadvantaged members."*

Ross Upshur, Jerome Singh and Nathan Ford in *Apocalypse or redemption: responding to extensively drug-resistant tuberculosis*.<sup>1</sup>

## Key points

- **Multi-drug resistant tuberculosis (MDR-TB) may be caused by failure to adhere to treatment, interrupted care, the presence of resistance to one drug at the beginning of first-line treatment, or an inadequate TB control programme. People can also acquire MDR-TB from others.**
- **Extensively drug-resistant tuberculosis (XDR-TB) may be caused by the failure of second or third-line treatment for MDR-TB, or it may be acquired from others. There have been outbreaks of XDR-TB in health facilities in South Africa.**
- **MDR-TB treatment lasts 18 months to 2 years. Hospitalising people for some or all of this time may contribute to failure of treatment, and to the spread of MDR-TB to others in poorly ventilated spaces, so it may be better to treat MDR-TB in the community.**
- **The frequency of MDR-TB in some regions of the world is probably underestimated due to lack of surveillance and laboratory tests to monitor drug resistance. Eastern Europe, Russia, China and India have many cases, but the frequency is also believed to be high in southern Africa.**
- **People with HIV may be more prone to develop MDR-TB, but it is difficult to tell whether it is HIV that places people at higher risk, or if it is due to the factors in their life that caused them to become infected with HIV.**
- **MDR-TB need not have a bad prognosis if it is diagnosed early and treated according to guidelines with the right drugs. Access to the appropriate drugs for MDR-TB is critical.**
- **XDR-TB tends to have a poor prognosis in people with HIV. Making sure that people with MDR and XDR TB start antiretroviral therapy immediately is likely to**

**improve the chances of survival. Having access to the widest choice of TB drugs is also likely to improve survival.**

- **Early diagnosis using drug sensitivity testing, prompt management of MDR-TB, positive and supportive health care worker attitudes and sound patient support for adherence are all essential components of the care package of people with HIV who have MDR or XDR-TB.**

## Towards more compassionate care for people with drug resistant TB and their caregivers

"The policy was to hospitalise people with multidrug resistant tuberculosis (MDR-TB) for four to six months or at least until culture conversion. That's fine if you have the capacity to do it," said Bruce Margot, who serves as the TB Control programme coordinator for KwaZulu Natal's (KZN) Department of Health (DOH). "But if you don't have the capacity, you can't implement the policy. It's as simple as that. And you've got patients waiting for treatment."

Dr Margot was speaking at the 2<sup>nd</sup> South African TB Conference (2<sup>nd</sup> SATB) during a roundtable discussion on the decentralised management of MDR-TB. He has been helping the province of KZN weather the fall-out after the [infamous outbreak of extensively drug resistant TB \(XDR-TB\) in Tugela Ferry](#).

"All of a sudden, we had double the number of cases. But you can't build hospitals in a couple of months, particularly government services," he said. Moreover, Mr Margot told the audience that hospital-based treatment of drug-resistant TB was associated with a very high default rate in the provincial health system because it simply wasn't practical from the patient's perspective – breadwinners with TB couldn't leave their families without any support, and mothers with TB couldn't leave small children at home alone.

"This was the point that nobody really had looked at, which has to do with case retention and keeping your patients in your programme."

So over the last couple of years, KZN has been exploring the decentralisation of MDR-TB care, moving away from requiring prolonged stays for people with drug-resistant TB at King George V Hospital (the 'centre of excellence' in the province), starting first with short stays (2-8 weeks) at MDR-TB units in district level hospitals and then, as soon as feasible, sending the patient home to receive community-based care provided either at local clinics or at home, during visits from mobile teams.

A similar move towards introducing community-based management of MDR-TB in order to expand access to care is now taking place at the national level in South Africa.

"We do not have an adequate number of hospital beds and welcome the opportunity to work with other partners to provide decentralised MDR-TB services," according to South Africa's Minister of Health, Dr Aaron Motsoaledi's official address to the conference.

"We know we need to move to more decentralised care, and the ministry of health is currently in the process of revising its policy," said Dr Norbert O. Ndjeka, Chief Director for TB Control and Management for the Health Department.

In fact, a draft policy on community-based MDR-TB care is being reviewed and is expected to be finalised within the year.

This move away from long-term involuntary hospitalisation represents a sea change in TB control policy for South Africa, where

people with drug-resistant TB have been known to riot against what they perceived as virtual incarceration in health facilities surrounded by barbed wire and policed by armed security guards. The relationship between healthcare providers and patients became antagonistic — and during several sessions at the 2<sup>nd</sup> SATB conference, nurses complained about being physically assaulted, and having clients with M/XDR-TB cough or spit upon them in an effort to give them the infection.

The old policy was more focused on curing the infection rather than caring for the individual, an obsession with disease containment and meeting TB control targets that paid too little heed to how it affected the quality of life of people and families affected by M/XDR-TB.

“Changing the focus from TB cure to TB care and working within a team where patients receive holistic care that includes TB treatment will not only improve compliance but will also help to support families during this difficult period,” wrote Krause, Gwyther, and Gould, who presented a poster on the palliative care of MDR-TB at the 2<sup>nd</sup> SATB Conference.

As regular HATIP readers know, palliative care is an holistic approach that should start as soon as a person presents for care, and that tries to alleviate the pain and suffering of people with, and families affected by a severe or life-threatening illness. In the case of M/XDR-TB, patients and their families have a right to maintain a reasonable quality of life over the entire course of illness regardless of the prognosis, or whether the patient is hospitalised or ambulatory. But access to emotional, spiritual and psychosocial support is generally better in the home.

And a growing body of evidence, from KZN, and the Ubuntu clinic in Khayelitsha, is showing that community-based care is not only more compassionate, it reduces costs and may be more effective. Similar models of care have also been explored in Lesotho, Nepal, India, and Peru — and current WHO policy is to assist countries in creating models of care that can both meet the needs of patients, and which are feasible and cost-effective in the health system.<sup>2</sup> Such models should be considered in other settings, such as Eastern Europe, where policies that require hospitalisation and fail to consider the patients' needs holistically are contributing to unprecedented high levels of MDR-TB transmission (see below).

But while providing decentralised care is a good first step towards more patient-centred care, as other presentations at the 2<sup>nd</sup> SATB conference illustrated, decentralising care for M/XDR-TB is not necessarily easy and presents a number of challenges in management and clinical practice. In fact, some studies found that funds for MDR-TB care were sometimes misused, and nurses complained of lacking any specialised training to deal with MDR-TB and having inadequate support from doctors.<sup>3</sup> As a result, guidelines were sometimes not followed, and some drug resistance actually worsened, becoming XDR-TB.

With this in mind, this HATIP will review what we know on TB drug resistance, why and where it happens, its relationship with HIV and what outcomes can be expected. Unfortunately, there is a high rate of treatment failure and death — particularly among people with HIV.

The second of the two articles on MDR-TB care will focus on existing models of care for M/XDR-TB, with a focus on materials that can help programmes and healthcare workers prepare for treating M/XDR-TB at the clinic or within the community, how to provide palliative and supportive care, with symptom relief and better management of drug side effects, and finally, in some cases, end-of-life care for the substantial proportion of those who fail treatment.

## Inadequate treatment leads to TB drug resistance

As soon as the first antibiotic (streptomycin) to fight TB became available in the 1940s, drug resistance began to evolve. Whenever a bacillus or virus is exposed to a drug or treatment that isn't potent enough to totally clear it, the microbe will continue to reproduce. Eventually, a mutation will occur that makes the bacilli less sensitive to the effects of treatment, and the microbe will flourish. This is essentially the reason why a potent combination drug regimen — attacking the bacillus on multiple fronts — is needed to stop TB.<sup>4</sup>

The current standard first-line regimen for TB ought to cure 95% of cases — provided that the full course of treatment is taken as recommended. However, whenever an active TB infection receives inadequate treatment, drug resistance can develop — and once it has, it can then be transmitted from one person to another.

Data suggest that having an mTB infection that is resistant to even one drug when starting a TB treatment regimen can reduce the chances of curing TB, increase the risk of relapse and the likelihood of further resistance developing to other drugs within the treatment regimen.<sup>5</sup> But it should also be pointed out that there are degrees of resistance to individual drugs or within drug classes.

For instance, many people with isoniazid 'resistance' have an infection which is less sensitive to standard doses of the drug, but which may still respond to higher isoniazid doses.<sup>6</sup> There are also accumulating data which suggest that moxifloxacin may work against TB that is resistant to some of the weaker fluoroquinolone drugs (see later in this article).<sup>7</sup>

Multidrug-resistant tuberculosis (MDR-TB) is defined as TB caused by mTB that has become resistant to at least isoniazid and rifampicin, the two most critical first-line anti-TB drugs (though resistance may develop to the other drugs in the regimen as well). And extensively drug-resistant TB (XDR-TB) is MDR-TB that is also resistant to any one of the fluoroquinolones and to at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin). Sometimes, MDR-TB that is only resistant to the injectable second line drugs is referred to as being 'pre-XDR-TB.'

Treating someone with MDR-TB and especially XDR-TB requires a longer course of therapy (eighteen months to two years) with drugs that are more expensive and toxic and yet less potent. Drug-resistant TB can be difficult to diagnose and respond to in a timely manner, but failure to put someone on a regimen that is effective against the TB they are infected with, and then support their adherence, can lead to poor outcomes and death — particularly in people with HIV — as well as onward transmission.

## Health system failures responsible for spread of M/XDR-TB

Epidemics of drug-resistant TB begin with a failure to effectively manage drug-sensitive TB. In the past, there was a tendency to blame the patient, but now more of the responsibility is being shifted to programmatic failures.

Consistently adhering to a long-term treatment regimen is difficult for anyone, but a range of social barriers and situations can make it more unlikely that a person will complete a course of treatment for MDR-TB.

People who are poorly informed about the need to take the whole course of treatment may quit or simply forget to keep taking it as soon as they feel well. People who are homeless, or live in remote

areas far from the clinic may not always make it to the clinic in time to pick up their supply of treatment, or a treatment supporter may have difficulty delivering treatment to them. Responsibilities at home and employment can get in the way of adherence. Alcohol and drug use have been associated with people not adhering to or defaulting on treatment – and this has been a particular problem in many countries of the former Soviet Union, such as Russia and Ukraine.

But ultimately, it is the responsibility of the national TB control programme (NTP) to take people's needs and foibles into account, and to find and implement culturally appropriate ways to support adherence and ensure that people with TB take all of their treatment. Many fail to do this, or worse, implement policies that discourage people from staying in care.

Partly for this reason, the emergence of M/XDR-TB is often said to be the result of a weak TB control programme. This is also the case when the NTP doesn't comply with evidence-based treatment guidelines, doesn't adequately train, supervise or monitor the clinicians treating TB, or the counsellor and community-based carers supporting treatment, if the NTP can't keep a consistent supply of high quality drugs in stock, or when it charges for treatment (choosing between food and TB care is a choice no one should have to make). Sometimes these failings are due to poor management, but often NTPs have become disorganised or have failed to update policies after periods of political upheaval, or economic or social crises that can disrupt health systems. The challenge is often one of political will – making health and TB control national priorities.

TB programmes may also lose track of a person's care due to migration, displacement or imprisonment when there are no mechanisms in place to ensure continuity of care. Prison systems in many countries are especially notorious for failing to follow TB programme guidelines, and sometimes operate as if prisoners have no right to health. Not only are treatment standards poor, but there is little to no infection control in the facilities, so both drug-sensitive and drug-resistant TB may be transmitted among the prisoners and the prison systems become reservoirs for dangerous forms of TB – which can have serious consequences for society when infected prisoners are released.

The majority of MDR-TB cases are due to infection with a drug-resistant strain (in other words, primary or transmitted resistance among new or relapse cases rather than acquired resistance). Failure to quickly find and treat M/XDR-TB cases – such as failing to do contact tracing on known cases – allows M/XDR-TB to spread in homes and in the community. Likewise, poor infection control in places where people at risk of drug-resistant TB are likely to gather or work ([such as in the mining industry](#)) put many at risk of infection. In some settings, policies requiring prolonged stays in TB hospitals contribute to primary transmission of M/XDR-TB. For example, [a study in Latvia found that hospitalising people with tuberculosis for long periods put them at increased risk of reinfection with multidrug-resistant \(MDR\) and extensively-drug-resistant \(XDR\)-TB strains](#) – contracted from other patients.

But infection control is not just the responsibility of the NTP. After the XDR-TB outbreak at the Church of Scotland Hospital (COSH) in Tugela Ferry, it was apparent that M/XDR-TB was being spread within the health system in South Africa, and that HIV programmes in particular needed to implement good infection control to prevent the spread of M/XDR-TB.

"One of the very first things that we recognised was that we were dealing with hospital transmission of XDR-TB," Dr Tony Moll of CoSH said at the 2nd SATB Conference in June.

Regardless of how resistance became established, it is the TB control programme's responsibility to perform surveillance to determine country- or setting-specific causes of drug resistance – in order to identify the most important targets for intervention.

### The spread of XDR at CoSH, and beyond...?

"We were getting HIV-positive patients coming in with an XDR diagnosis and they had never had TB before," Dr Tony Moll told the audience at the 2nd SATB, describing the outbreak of XDR-TB at the Church of Scotland Hospital. In fact, 51% of the XDR-TB cases at CoSH had received no prior TB treatment. Community contact tracing revealed very few contacts becoming XDR-positive – however, about 61% of the original cases had been hospitalised at the facility in the previous two years.

Dr Moll presented a recent analysis showing that there was at least one undiagnosed XDR-TB patient (and a median of three) in the hospital for 661 days out of the 730 days (91 percent) during that two-year period from 2005-2006 – and two-thirds of patients had been hospitalised prior to their developing XDR-TB.

"Out of 148 patients, 80 (68%) were smear positive. 115 (78%) were hospitalised at the same time as a known XDR-TB patient. The median number of cases that patients were exposed to was six [IQR 3-8]. And there was a median duration of 40 patient days of exposure," he said.

Genotyping found a similar strain in 83% with a known molecular fingerprint pattern. The fact that eight healthcare workers at CoSH also died of XDR-TB was yet another indication that it was being spread inside the healthcare facility.

Finally, [improving infection control at the facility reduced the incidence of TB at CoSH](#). Dr Moll noted that for a few years, there had been more XDR-TB diagnosed than MDR-TB, but since implementing better infection control "for the first time we've seen that switch around to a sort of a normal ratio where there is XDR less than MDR."

But he cautioned the audience that an XDR-TB outbreak could easily happen again tomorrow elsewhere in the country.

"What happened at Tugela Ferry at the Church of Scotland Hospital - the ingredients of that environment - are in fact present in many of our rural hospitals and in many of our city hospitals and outbreaks similar to what we experienced could very, very easily happen in other settings," he said.

Indeed one poster described a qualitative study into the quality of care in the South African MDR and XDR-TB hospitals. "None of the facilities visited had isolated XDR-TB patients from MDR-TB patients. None of them had enough space – they all had waiting lists of patients for beds," the authors wrote.<sup>8</sup>

There are some preliminary indications that something like an outbreak is happening in the Eastern Cape but it doesn't seem to be from nosocomial transmission – at least not yet. A poster presentation from the Medical Research Council of South Africa described the results of drug sensitivity testing (DST) in 133 people from the province who entered an MDR-TB study – almost half were resistant to three injectable second-line drugs (which is thus considered to be a pre-XDR-TB strain).<sup>9</sup> The cases are believed to be primary resistance because none of the subjects had previously been treated with second-line drugs. However, they came from all over the province (from 42 different referral facilities).



According to the most recent surveillance report from WHO, only 1.8% of the new incident TB cases in South Africa are M/XDR-TB (primary resistance that has been transmitted). In contrast to the COSH cohort, Dr Keertan Dheda of the University of Cape Town, who was also at the 2<sup>nd</sup> SATB conference, presented data from four other South African sites (in which 81% of the XDR-TB was acquired rather than primary resistance) and many of these had become smear-negative while still on MDR-TB treatment – and thus not believed to be so highly infectious.

However, another study in which Dr Dheda is involved does suggest that drug-resistant TB is being spread in the hospitals.

"We went to King George Hospital and went back to the case records over the last 6 years to look at how many healthcare workers were treated at [the hospital]. And to our surprise, there were 208 MDR-TB cases and 23 XDR-TB cases all in healthcare workers. MDR/XDR-TB was six times more common in healthcare workers in KwaZulu-Natal compared to the general population. For that reason, we speculate that much of this disease was contracted at the workplace," he said.

### Global and regional burdens of M/XDR-TB

MDR-TB began to be seen as an international public health threat in the early 1990s. [A global surveillance system for TB drug resistance was then established and has since documented a rapidly increasing burden of both MDR- and XDR-TB – as well as extremely poor outcomes in people with TB resistant to second line drugs.](#)<sup>10</sup>

According to the most recent WHO surveillance report, there are approximately 440,000 (range 390 000–510 000) new cases of MDR-TB – 3.6% (95% confidence interval (CI): 3.0–4.4) of all the incident TB cases – each year. The estimate of new cases in the report is slightly lower than in previous years, not because there is less MDR-TB, but because new data have become available and there have been changes in the modelling methodology.

The total number of (prevalent) cases worldwide could be two to three times higher since some people with MDR-TB may survive for several years with the disease.<sup>11</sup>

XDR-TB estimates are more difficult to come by, but 57 countries and territories had reported at least one case of XDR-TB by November 2009. XDR-TB made up about 5.4% of the MDR-TB burden among those countries that have reported continuous surveillance or representative surveys of second-line drug resistance among MDR-TB cases. But the proportion is higher in some countries; for instance, 10.5% of the MDR-TB cases in South Africa are believed to be XDR-TB.

Since there are so many situations where drug resistance can evolve, there are significant regional variations in the burden and pattern of M/XDR-TB. WHO categorises 27 countries as being high MDR-TB burden countries, either because they have a large absolute number of cases, or because at least 10% of newly registered cases are MDR-TB (excluding countries with very low case loads of TB).

With huge numbers of people with TB, China and India are believed to have the highest absolute number of MDR-TB cases, and together are responsible for almost half of the global burden.

The Russian Federation produces the next highest number of incident MDR-TB cases, ~38,000. Along with Bulgaria, many of the countries that were part of the former Soviet Union are included as high-burden countries solely because more than 10% of the new cases are drug-resistant TB. In fact, according to the most recent WHO surveillance report, in 2008, between 23 and 28% of all new TB cases in Archangelsk, Pskov and Murmansk (north-western

Russia) were multi-drug resistant, the highest proportion ever reported anywhere in the world

Although there has been a reduction in the incidence of MDR-TB, and some Eastern European settings have brought their practice into line with international guidelines, the antiquated and crumbling Soviet TB control services are still entrenched in some areas. In particular they are failing to address the need to integrate TB care with treatment for drug dependency (opioid substitution therapy) for the large population of people who inject drugs in some of those countries. For instance, in Ukraine, injecting drug use has been shown to be highly associated with MDR-TB.<sup>12</sup>

But in many parts of the world, it is difficult to say how much M/XDR-TB there might be because of the lack of laboratory capacity to do drug sensitivity testing (DST) and other barriers to performing surveys. Notably, less than 30,000 (7%) of the estimated global burden of MDR-TB cases in 2008 was actually diagnosed and notified. Surveillance information from many countries is quite old and the quality poor so WHO models often had little or mediocre data to go on.

A case in point is the estimated incidence of MDR-TB in Africa: WHO estimates that there are 69,000 (95% CI: 53 000–110 000) new cases per year. Although Nigeria and the Democratic Republic of Congo (DRC) rank along with South Africa and Ethiopia among the 27 high-burden MDR-TB countries, there are no national surveillance data available for either country. In fact, of the 46 countries in the African Region, only 12 have conducted a nationwide survey since 2000 and only South Africa provides continuous surveillance (though the quality of those data are not yet optimal since cultures are only performed on about 40% of notified cases and DST on about 55% of positive cultures).

"The burden of anti-TB drug resistance in the African Region remains largely unquantified," says the recent WHO report. "Nevertheless, given that African countries have the highest incidence rate of TB in the world, even at low proportions of drug resistance the caseload of MDR-TB patients becomes very high. As a result the rates of MDR-TB cases arising per 100,000 population in some southern African countries are 5–6 times higher than those of China and India."

But it might be even higher. If estimates are correct, South Africa has the fifth highest burden of MDR-TB in the world, with an estimated 13,000 (95% CI, 10–16,000) new cases per year, 1.8% (95% CI 1.5–2.3%) of the new TB cases, and 6.7% (95% CI 5.5–8.1%) of the retreatment cases. However, at the 2<sup>nd</sup> TB conference, it was reported that 9000 MDR-TB new cases were diagnosed in South Africa in 2009. But given the rather mediocre uptake of culture and DST, it strains credulity to think that the country is truly identifying around three-quarters of the new MDR-TB cases.

Although the total case burden is much higher, the estimated incidence rate of MDR-TB in South Africa is reported to differ little from some of the countries in Western Europe – which is surprising given South Africa's lower treatment success rate and much higher default rates on first-line TB treatment (particularly in some parts of the country). Notably, according to recent survey results (presented at the 40<sup>th</sup> Union World Conference of Lung Health in Cancun in December 2009) incidence rates in three neighbouring countries, Namibia, Mozambique and Botswana are at least two times higher than in South Africa.

In the 2008 Namibian survey, 100 MDR-TB cases were identified out of 1451 smear-positive cases, 6.9% of the overall TB cases, (95% CI 5.7–8.3%). The incidence rate was 3.8% (95% CI 2.8–5.1%) in the new TB cases, and 16.4% (95% CI 12.9–20.6%) among previously

treated cases.<sup>13</sup> Between 2006 and 2007 in Mozambique, a similar survey found an MDR-TB incidence rate of 3.5% (95 CI 2.5–4.7%) among new TB cases, and 11.2% (95 CI 4.2–30.0%) among retreatment cases — and the researchers noted an increasing trend in resistance since the last survey in 1999.<sup>14, 15</sup>

In Botswana, a survey conducted from September 2007–May 2008, found an MDR-TB incidence rate of 3.4% among new TB cases (95 CI 2.4–4.8%) and 13.1% of retreatment cases (95 CI 8.6–19.6%). Since the previous survey in Botswana in 1999, there has been an increasing trend in resistance to the first-line TB drugs, including a greater than 4-fold increase in MDR-TB among the new TB cases.<sup>16</sup>

Recent data from some cohorts in South Africa have also found much higher levels of drug resistance. For instance, [a cross-sectional survey in Khayelitsha found 7.9% rifampicin resistance \(which usually goes hand in hand with isoniazid resistance\) among 544 individuals diagnosed with culture-positive TB, 4.5% of the new TB cases and 10.8% of previously treated cases.](#)<sup>17</sup>

Another recently published study assessed the burden of M/XDR-TB among TB suspects in Phidisa, an observational and randomised HIV treatment study, involving members of the South African military and their families. Out of 584 people with HIV and complete culture results, 107 were found to be culture positive for TB — [20.6% of these had MDR-TB, 11.9% among new cases, 27.1% among those who had previously been treated.](#)<sup>18</sup>

It's not clear that these cohorts can be considered representative of South Africa as a whole, however.

"It is entirely possible that the Khayelitsha and other cohorts reflect problem areas or outbreaks," Dr Karin Weyer of WHO's STOP TB Department told HATIP. Even so, she isn't certain about the estimates either.

"I have always felt that the estimated case load [for South Africa] was too low. That seems to be borne out now by the results from much more systematic culture and DST having been implemented. The 9000+ cases reported by the NHLS is entirely realistic yet still a significant under-count because health care staff are not yet requesting culture and DST for all cases at risk as defined in the NTP strategy," she said.

## How do HIV and drug-resistant TB interact?

One factor that could have great bearing in Africa is whether there is an association between MDR-TB and HIV. It is well established that HIV infection increases the risk of developing TB, so to the extent that people with HIV are exposed to it, the HIV epidemic would be expected to increase both the absolute number of drug-resistant TB cases as an effect of the larger number of drug-sensitive TB cases occurring due to immunosuppression. But does HIV further exacerbate the incidence of TB drug resistance by other mechanisms?

There are several reasons to be concerned that it might, though the evidence is unclear or conflicting.

For instance, it has been postulated that people with HIV who are taking TB treatment may be exposed to suboptimal drug levels because of HIV-related malabsorption or altered metabolism of the medications.<sup>19</sup> [A pharmacokinetic study in Botswana found low concentrations of TB drugs in people with HIV.](#) It is also possible that resistance may be more likely to be acquired when the immune system cannot contribute to fighting off the infection.

In one study in the US, researchers noted an increased incidence of acquired rifampicin resistance among people with TB and untreated HIV.<sup>20</sup> Notably South Africa's 2002 MDR-TB survey, which

didn't observe any significant overall difference in HIV prevalence among those with drug-resistant and drug-sensitive TB, did find rifampicin mono-resistance in 31 people. Seventeen of these were retreatment patients — 15 of whom were HIV-positive.<sup>21</sup> However, in Dr Cox's study in Khayelitsha, rifampicin resistance was independently associated with female gender and previous treatment but not HIV status; (even though people with HIV had a higher prevalence of resistance to rifampicin than HIV-negative patients (9.3% vs. 5.5%), the difference did not achieve statistical significance).

A 2009 meta-analysis could find no consistent link between HIV and the risk of acquired resistance in 8 studies.<sup>22</sup> However, the studies available for this analysis were a bit of a mixed bag, with differing designs, and researchers didn't always take confounding variables into account, like shared risk factors such as high rates of injecting drug use, alcoholism, incarceration, social marginalisation and lack of access to medical care. For instance, some studies have reported that people coinfectd with HIV and TB in Ukraine, Estonia, Latvia, Lithuania and the Republic of Moldova are at greater risk of MDR-TB — but there are a number of possible confounding variables in these populations. [In Ukraine](#), without opioid substitution therapy, people who inject drugs (PWID) are both more likely to become HIV-infected because of sharing contaminated equipment, and to adhere poorly to TB treatment.

Even so, while HIV may not be the sole reason for a higher burden of MDR-TB in people with HIV, in some concentrated HIV epidemics, the confounding variables that increase the risk of drug-resistant TB are also what make people susceptible to HIV in the first place.

Another issue that makes it difficult to gauge HIV's impact is that many of the studies have been cross-sectional surveys that looked only for the prevalence of MDR-TB in a population within a short timeframe. But if people with HIV and drug resistant TB are dying faster (and most data suggest they do), often before presentation for care or diagnosis or DST, then a cross-sectional study might miss an increased incidence in that population. Also, people with HIV are more likely to be smear-negative and less likely to be diagnosed and reported (since they are considered less infectious, many NTP surveys don't even include smear-negative cases). Finally, another confounding variable is that, adherence support and the development of resistance could be different from study to study because of profound differences between how programmes manage and/or support people with HIV at a site or within a community.

That being said, the meta-analysis did suggest that HIV infection is associated with more primary MDR-TB, with a prevalence ratio of 2.72 (95% CI 2.03, 3.66) in the twelve included studies.

Even if there is no direct interaction between MDR-TB and HIV, the impact of the HIV epidemic on the total TB burden overall has led to the utter collapse of TB control in some places.

If poor TB management does indeed cause drug resistance, these failures could be expected to result in an increasing relative burden of drug-resistant TB. But it is difficult to find clear evidence that this is happening.

For instance, the rapidly increasing number of diagnosed cases in South Africa might just reflect improved lab capacity and case detection. Unfortunately, with the exception of the recent preliminary data from Mozambique and Botswana, there are few reliable longitudinal or continuous surveillance data to document whether drug resistance is in fact on the increase in countries with a high burden of HIV.

But where TB control has failed, leading to an increase in, and transmission of, acquired drug-resistant TB, the impact is likely to

be felt first by people with HIV, because HIV infection shortens the time to developing active TB after exposure. In other words, an increase in the transmission of acquired M/XDR-TB would be more rapidly reflected, as the meta-analysis has found, in an increased burden of primary M/XDR-TB in the HIV-positive community — which, tragically, may be something like canaries in the mine. Compounding this risk is the fact that people with HIV are more likely to utilise the health services where they could come into contact with people with M/XDR-TB (if there is poor infection control). Outbreaks of drug-resistant TB among people with HIV, such as the one in Tugela Ferry, are well documented, and provide clear evidence that this is happening.

Whether higher drug resistance in people with HIV will then become further amplified may depend on how infectious these cases of M/XDR-TB are. For the periods before these cases are unrecognised as being drug resistant, some HIV-positive individuals MDR-TB can be highly infectious, [according to a guinea pig study by Dr Rod Escombe in Peru](#).<sup>23</sup>

In a modern day repeat of the classical TB airborne transmission study, in which guinea pigs are exposed to air expelled from a TB ward, Dr Escombe found that just 9% of HIV-positive patients with TB were the source of 98% of the TB infections observed in the guinea pigs. Almost all of the TB that was transmitted was MDR-TB, even though there were both drug-sensitive and drug-resistant TB patients in the ward.

“There is every reason to believe that the full brunt of MDR-TB still has to be felt in South Africa,” wrote Weyer et al last year. “Although it is difficult to accurately predict the impact of the HIV epidemic on MDR-TB, weaknesses in TB control stand to be brought into sharp focus should these two epidemics coincide.”

“We don’t know the magnitude of HIV/MDR-TB co-infection,” said Dr Haileyesus Getahun of WHO’s STOP TB Department, in a recent WHO Bulletin, “but what we know is that the outcome of such a combination is deadly to patients.”<sup>24</sup>

## Variations in prognosis of M/XDR-TB, and risk factors for poor outcomes

One of the things that was so shocking about the initial outbreak of XDR-TB in Tugela Ferry was that 98% of XDR-TB patients coinfecting with HIV died, with a median time of death of only 16 days from the time of specimen collection for DST — well before a diagnosis of drug-resistant TB could be obtained.<sup>25</sup>

Since that time, there has been some debate on whether the prognosis of M/XDR-TB is always so consistently bad in people with HIV and how much can it be improved by early case detection, and aggressive treatment with second- or third-line TB treatment and ART?

One thing to keep in mind is that, according to the recent WHO surveillance report, “less than 3% of the estimated total number of MDR and XDR cases of TB receive treatment according to WHO recommended standards.” For the remaining 97% of 440,000 estimated people with M/XDR-TB, (most of whom are undiagnosed) outcomes can be expected to be poor. WHO estimates that MDR-TB caused about 150,000 deaths in 2008.<sup>26</sup>

Standards for treatment of MDR-TB differ widely between countries, but even for people who live in the European Union, receiving an MDR-TB diagnosis was strongly associated with the risk of dying from any cause (adjusted OR=3.9, 95% CI 3.3–4.6) after adjustment for confounders such as age, sex, and previous anti-TB treatment. According to the recent WHO MDR-TB surveillance report, the overall success rate for MDR-TB treatment was 60% (95% CI

55–66%) (roughly half of the remainder die or fail treatment, while the other continue treatment or are transferred). These results were probably strengthened somewhat due to the efforts of a programme known as the Green Light Committee, which was established to increase access of appropriate second-line TB therapy for people with MDR-TB.

XDR-TB can take even longer to recognise, and effective treatment regimens are more difficult to assemble. Along with Tugela Ferry, some of the earliest reports were of poor outcomes, such as in Estonia.<sup>27</sup> However, a number of programmes have reported better success treating XDR-TB. [With aggressive treatment, a project set up in Tomsk, Russia achieved a cure or treatment completion in two-thirds of the people with MDR-TB \(n= 579\) and almost half of those with XDR-TB \(n=29\).](#)<sup>28</sup>

The programme was the result of a partnership between the regional TB programme, local prison services, and the NGOs Partners in Health and the Open Society Institute, who equipped a laboratory to carry out DST. Individual treatment regimens (ITRs) were chosen using a standard algorithm based on DST results and their previous treatment history. The rate of mortality in this small cohort was only 7%. Some of the participants were prisoners, the remainder were hospitalised for the period they were on parenteral therapy.

In a South Korean study, involving 155 people, 132 with MDR-TB and 27 with XDR-TB, 66% of the participants were cured or completed treatment — and there was no difference between MDR-TB and XDR-TB in positive outcomes.<sup>29</sup> Again early aggressive treatment with an individualised treatment regimen based on drug sensitivity testing (including at least 4 effective drugs), was associated with better results. In addition, surgical resection, a procedure in which lung tissue containing infected lesions or cavities is surgically removed, was performed in subjects who were not responding to treatment (including almost half of the people with XDR-TB) and was associated with improved outcomes. For the most part, treatment was provided on an outpatient basis.

Mitnick et al reported similar results in a study from Peru that included 651 subjects, 48 with XDR-TB and 603 with MDR-TB.<sup>30</sup> Based on treatment and contact history, the initial treatment regimen was empirical and then individualised based upon DST results with the goal of using at least 5 drugs to which the individual was susceptible, including cycloserine, an injectable drug, and a fluoroquinolone. 29 (60.4%) of those with XDR-TB completed treatment or were cured, which was almost as good as in MDR-TB (400 patients (66.3%)). Community health workers supervised daily ambulatory treatment, though patients could be hospitalised if warranted.

Another Peruvian study described poorer outcomes when regimens for people with XDR-TB were started before diagnosis and DST results, with 17(46%) cured, 8 (22%) deaths and 11(30%) who either failed or defaulted treatment.<sup>31</sup> However, in 14 XDR-TB cases who received a diagnosis before ITR treatment initiation, 10 (71%) were cured and the median conversion time was 2 months.”

Notably, none of the people with XDR-TB in the Tomsk, Korean or Peruvian studies had HIV — and even when it isn’t cured, the course of disease seems to be somewhat tempered by aggressive treatment.

“Unlike XDR tuberculosis in populations with high rates of HIV, most patients in our cohort with poor treatment outcomes did not die, but continued to be ill (treatment failures or defaulters),” wrote Keshavjee et al.

“Our data show that in the absence of HIV, XDR-TB is a treatable disease,” wrote Bonilla et al.



In an editorial that accompanied the report from Toms, Drs Helen Cox and Cheryl McDermid, who work with Médecins Sans Frontières in South Africa noted, "We should be cautious in our hope to attain such success rates in settings with a high prevalence of HIV."<sup>32</sup>

But in South Africa, outcomes seem worse — even in people without HIV. According to a study from the Western Cape, which included 486 people with MDR-TB who started treatment, only 49% were cured, while 29% defaulted, and 14% died even though less than 10% were HIV-positive in the cohort.<sup>33</sup>

Another study presented at the 2nd SATB Conference analysed relative survival and found a very high rate of mortality among people with MDR-TB and HIV.<sup>34</sup> The study included 2079 people with MDR-TB who enrolled in a standardised MDR-TB treatment programme in South Africa between 2000 to 2004, and followed for up to two years. HIV status was only available for about two-thirds of the participants, but 26.65% were known to be HIV positive, and these had a 6.183 excess hazard ratio (95% CI 3.223-12.86). Of course, not all of these deaths are necessarily attributable to MDR-TB (especially over a couple of years of follow-up) since HIV status is an independent risk predictor of mortality.

In the Tugela Ferry cohort, Dr Moll shared the results of an analysis of M/XDR-TB survival from 2005-2007, which found very poor outcomes when the analysis includes people who had drug-resistant TB that wasn't diagnosed in time for treatment initiation.

"At 30 days, there was an MDR-TB mortality of 40% and an XDR-TB mortality of 50%. So really, before these patients could be started on treatment or before their result actually was available to us as healthcare workers, these patients had already demised. The overall MDR-TB mortality was 71% and the XDR-TB mortality was really high at 83%," he said. But he also presented a separate analysis for survival after sixty days — after culture and DST result come back and more effective treatment can be initiated.

"Sixty days is important because that is more or less the time that we get our culture results back and the time that we can initiate treatment on these patients. By then, the survival after sixty days for MDR is 60% and your survival for XDR is 43%. These numbers would be very similar to the numbers that you would be getting from the tertiary hospitals - in other words, these are patients that have survived up to the time that their results come out and they survived to the time where you can initiate treatment. There's already a survival bias for these guys that reach the tertiary hospitals."

This was a reference to Dr Dheda's recently published study that found somewhat better outcomes overall in 174 people diagnosed with XDR-TB elsewhere in South Africa, with a 12-month mortality rate of about 36%, and an overall mortality rate of about 42%. Fifty-two percent of the cohort was HIV-negative but there was no difference observed in mortality between people with or without HIV.

"I'm not really sure, why, even in the HIV patients, our mortality was not as bad as in the Tugela Ferry outbreak," said Dr Dheda during another presentation. "I think those patients did have more advanced immunosuppression. There may be strain differences, the drug resistance profiles may be very different. The issue of [what TB drugs] were available etc. So there's a whole bunch of reasons... we found no significant difference in death in HIV compared to HIV-uninfected patients, but I think this is just a bias of our retrospective studies. It's very likely in fact that many HIV-infected patients died very quickly and were not captured by our study."

However, those who made it into the study had much higher CD4 cell counts than the people in Tugela Ferry and many went on to ART anyway. About 29 out of 82 people with HIV started on ART with a median CD4 cell count of 277 (160-365), while those who did not had a median CD4 count of 477 (170-477). But despite that high CD4 cell count, those who started ART had dramatically fewer deaths (0.38, 0.18-0.80;  $p=0.01$ ).

"Highly active antiretroviral therapy, despite its overlapping toxicity and adverse effects with antituberculosis drugs, and the high pill burden, substantially improves survival in patients with concomitant HIV/AIDS and XDR tuberculosis, and was generally well tolerated. Our data suggest that highly active antiretroviral therapy should be used at an early stage in patients with HIV infection and XDR tuberculosis."

Note, *earlier this year, South Africa announced that all M/XDR-TB patients with HIV infection qualify for ART regardless of CD4 count.*

Having more effective drugs available to add to a treatment regimen also made a difference. Dr Moll noted that in Tugela Ferry, there were clear differences in survival depending upon how many drugs a person was resistant to.

"As you increase the number of drug resistance patterns that the person has, the mortality increases until you get the worse mortality of the six-drug resistance pattern," said Dr Moll.

Or in other words, the more resistance there is, the fewer effective drugs in the treatment regimen. Of note, 2nd-line DST had been discontinued in 2002 in South Africa, following the implementation of the WHO-recommended standardised MDR-TB regimens (rather than individualised treatment regimens). But following the outbreak in Tugela Ferry, 2nd-line DST again became available and in January 2007, capreomycin and para-aminosalicylic acid (PAS) also became available for treatment.

Over time, survival could also be improving. In the Tugela Ferry cohort, one-year MDR-TB survival was 76%, in 2005. By 2007, it had improved to 55%. XDR-TB survival at one year went from 85% to 75% in 2007.

"By year, the mortalities of MDR-TB have definitely improved," said Dr Moll. "We started treatment earlier as we found the cases earlier and as we put the patients on treatment earlier. But the difference was not so marked with XDR, just because of poor treatment options."

"The more drugs you used in the regimen the better the patients did," said Dr Dheda of his study. He noted that later in the study, the drug moxifloxacin became available for treatment in the Eastern Cape and some NGO-supported institutions — and had a significant impact.

"No matter how we analyse the data, whether in HIV-positive or HIV-negative, and by doing all sorts of sensitivity analysis and limiting the data and correcting with all sorts of things — moxifloxacin still came out as an independent predictor of survival in these patients, which by definition are fluoroquinolone-resistant. So there is in fact data suggesting that there's incomplete cross-resistance within the fluoroquinolone class," said Dheda.

But even though Dr Dheda's cohort had better outcomes than in Tugela Ferry, he is no optimist about treatment. In addition to having a much worse survival than the studies in Peru, the culture conversion rate was only 19% (33/174). There was no difference in culture conversion in HIV-infected and HIV-uninfected people). The median time to conversion was also much longer (only 70% of those who had a culture conversion had done so by six months) — compared to culture conversions within two or three months in Peru.



Dr Dheda said that 14 of the culture conversions were in the Western Cape, and they have recently gone to see what had happened to those people.

"About one-third of those patients have died (most of these patients are HIV-negative) and another third in fact have reverted. So in fact even if your patient converts with XDR-TB, frequently culture reversion may occur in the South African setting," said Dr Dheda. In the South African setting, the outcomes are poor and the disease, in my opinion, is virtually untreatable and this is despite adherence to therapy, accessibility to surgery and intensive therapy."

Dr Moll concurred. "MDR-TB survival improves after diagnosis because there are treatment options available. XDR-TB survival does not improve, and the lack of effective treatment options leaves patients to suffer the natural history of TB disease."

Dr Dheda theorised that perhaps the long duration of TB and prior TB treatment before XDR-TB diagnosis could be a factor that could explain why even HIV-negative South African outcomes are worse. One clear negative predictor of culture conversion in the study was weighing less than 50 kg. This raises questions about wasting and malnutrition. One audience member remarked that nutritional support might be an essential adjunctive therapy, and may actually be the real reason why industrialised countries achieve better outcomes.

But it is worth pointing out, that perhaps the hospitalisation model of care is partly to blame for the poor outcomes – and there is a chance that adopting community-based care in South Africa could speed the time to getting on effective treatment (rather than waiting for a bed to become available), and provide the person with M/XDR-TB with more love and support.

## Implications

"So what are the implications?" said Dr Moll? "We have to go back to our mantra: find, treat and prevent."

"In order to succeed and scale-up treatment capacity for MDR-TB and HIV, we need collaboration between the TB and HIV programmes," said Dr Nesri Padayatchi of Caprisa during a plenary talk at the 2nd SATB conference. "All of the studies relating to mortality in MDR-TB have shown that late diagnosis, poor management of MDR-TB, healthcare worker attitude and support, and limited access to ART, all impact on treatment outcome. So it's automatic then that early diagnosis, prompt co-treatment of HIV/MDR and sound patient support - all of these are essential components of a comprehensive package of care for HIV-related MDR-TB. And BOTH TB and HIV programmes MUST prioritise this."

*Part two of this HATIP will address recent findings on the management of the condition, including case finding, diagnosis and DST, models of care for people with M/XDR-TB, the clinical and palliative care of TB.*

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