

CHAPTER 2

Drug resistance in tuberculosis – an overview

2.1. Anti-tuberculosis drugs

The history of anti-tuberculosis chemotherapy began in 1944 with the discovery of streptomycin. Since then, several agents have been discovered to have activity against *Mycobacterium tuberculosis*. A summary of the most commonly used TB drugs is provided in TABLE 2.1.

TABLE 2.1 Summary of key antituberculosis drugs (according to WHO group system)

Group	Description	Drug	Abbr	Site/mode of action	Genetic resistance
1	First-line antituberculosis drugs	Isoniazid	H	Mycolic acid synthesis	<i>inhA, katG</i>
		Rifampicin	R	RNA polymerase	<i>rpoB</i>
		Ethambutol	E	Cell wall polysaccharides	<i>embA, embB</i>
		Pyrazinamide	Z	Intracellular acidification	<i>pncA</i>
2	Injectable antituberculosis drugs	Kanamycin	Km	Protein synthesis (ribosome)	<i>rrs, eis</i>
		Amikacin	Amk	Protein synthesis (ribosome)	<i>rrs</i>
		Capreomycin	Cm	Protein synthesis (ribosome)	<i>rrs, tlyA</i>
		Streptomycin	S	Protein synthesis (ribosome)	<i>rrs, strA, S12</i>
3	Fluoroquinolones	Ofloxacin	Ofx	DNA gyrase	<i>gyrA, gyrB</i>
		Levofloxacin	Lx	DNA gyrase	<i>gyrA, gyrB</i>
		Moxifloxacin	Mfx	DNA gyrase	<i>gyrA, gyrB</i>
4	Oral bacteriostatic second-line antituberculosis drugs	Ethionamide	Eto	Mycolic acid synthesis	<i>ethA, inhA, katG</i>
		Cycloserine	Cs	Cell wall synthesis	?
		Terizidone	Trd	Cell wall synthesis	?
		<i>p</i> -aminosalicylic acid	PAS	Folate biosynthesis	<i>thyA</i>
5	Drugs with unclear efficacy	Clofazimine	Cfz	Not known	?
		Linezolid	Lzd	Protein synthesis (binds to rRNA)	?
		Co-amoxiclav	Amx/Clv	Cell wall synthesis	?
		Clarithromycin	Clr	Protein synthesis	?
		Imipenem	lpm	Cell wall synthesis	?

2.2. The history of drug resistance in tuberculosis

Drug resistance in tuberculosis became evident very early after the introduction of anti-tuberculosis chemotherapy. The first randomised controlled trial of streptomycin by the UK Medical Research Council (MRC) showed that streptomycin resistance developed early during treatment (of those evaluated, 85% developed phenotypic resistance in median 45 days) and compromised the clinical efficacy of streptomycin monotherapy¹. Subsequent trials involving streptomycin, para-aminosalicylic acid (PAS), and isoniazid demonstrated that the development of resistance was reduced by the use of combination therapy². Thus was born the concept of combination anti-tuberculosis chemotherapy. The introduction of rifampicin and pyrazinamide later allowed for shortening the duration of treatment, ultimately to six months.

In South Africa the use of effective combination chemotherapy led to a reduction in incidence of TB disease between the 1960's and 1990's and simultaneously led to a reduction in prevalence of drug resistance³. The national drug resistance surveillance programme documented a reduction in isoniazid resistance in all TB cases from 28.8% in 1965-1970 to 14.2% in 1980-1988 and a reduction in rifampicin resistance from 6.4% to 1.8% over the same periods³. Up to the mid-1990's combined resistance to rifampicin and isoniazid (multidrug resistance or MDR) was documented through surveillance programmes to be present in fewer than 2% of TB cases³.

Short-course treatment including both rifampicin and isoniazid became a key component of the WHO DOTS (Directly Observed Treatment, Short-course) programme introduced in the 1990's⁴. In Southern Africa, this coincided with the early phase of the HIV epidemic, which led to huge growth in the number of TB cases and which put TB programmes and health systems under enormous strain (FIGURE 2.1). This created an environment for the development and spread of drug-resistant strains. The increasing burden of multidrug-resistant TB (MDR-TB) in TB control programmes in South Africa was reported in the late 1990's⁵.

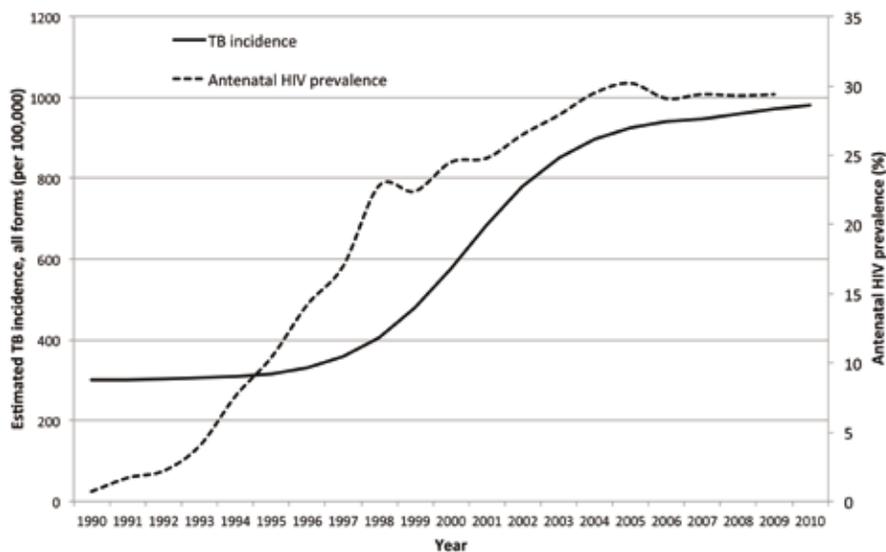


Figure 2.1 Estimated TB incidence (all forms) and ante natal HIV prevalence for South Africa 1990-2010 [Taken from source website: Health Systems Trust (www.hst.org.za)]

KwaZulu-Natal province in South Africa then fell under the spotlight in 2006 when an outbreak of extensively drug-resistant TB (XDR-TB), defined as MDR plus resistance to a fluoroquinolone and at least one second-line injectable agent, was reported amongst HIV-infected individuals in Tugela Ferry, uMzinyathi district⁶.

2.3. Epidemiology of drug-resistant TB in Southern Africa

The true burden of drug-resistant TB in southern Africa remains to a certain extent unknown⁷. Few countries have conducted nationwide surveys of TB drug resistance, and even fewer have repeated these surveys to monitor trends. Botswana is one of the few countries to have performed serial nationwide surveys. The results of the four surveys carried out between 1995 and 2008 (for proportion of TB cases with MDR-TB) are displayed in FIGURE 2.2⁸⁻¹².

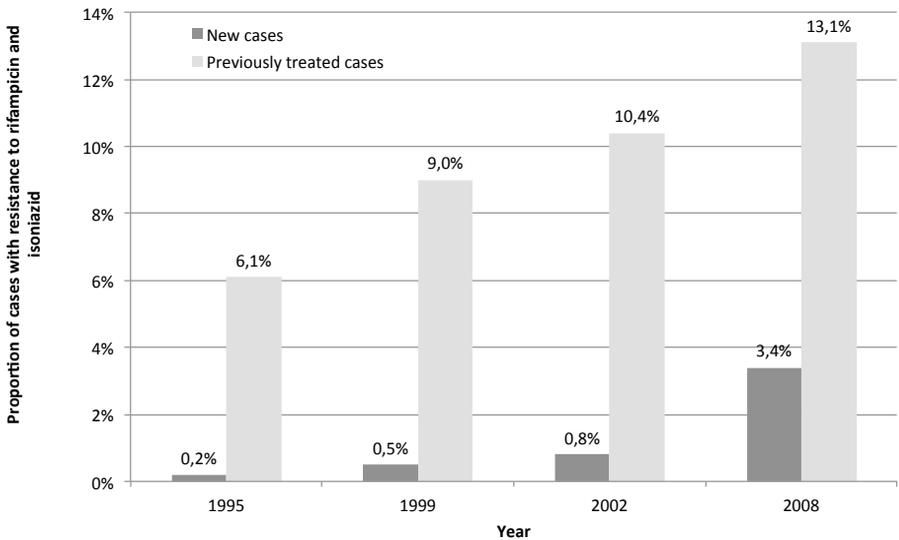


Figure 2.2 Proportion of new and previously treated TB cases with multidrug resistance (resistance to rifampicin and isoniazid) in Botswana national drug resistance surveys⁸⁻¹²

The last nationwide drug resistance survey in South Africa was performed in 2002. The proportions of new TB cases and previously treated TB cases with MDR-TB were 1.6% and 6.6% respectively¹³. South Africa has more recently relied on monitoring of routine laboratory data, which is prone to overestimation of the true burden of drug resistance (as culture/DST specimens are more commonly submitted for individuals with pre-existing risk of drug resistance). Despite this, the proportion of culture-positive isolates that are MDR has been fairly stable at ~5% between 2007 and 2011¹⁴. Even with this relatively low proportion of MDR-TB, the high TB incidence rates lead to a high absolute number of MDR-TB cases in South Africa (FIGURE 2.3)

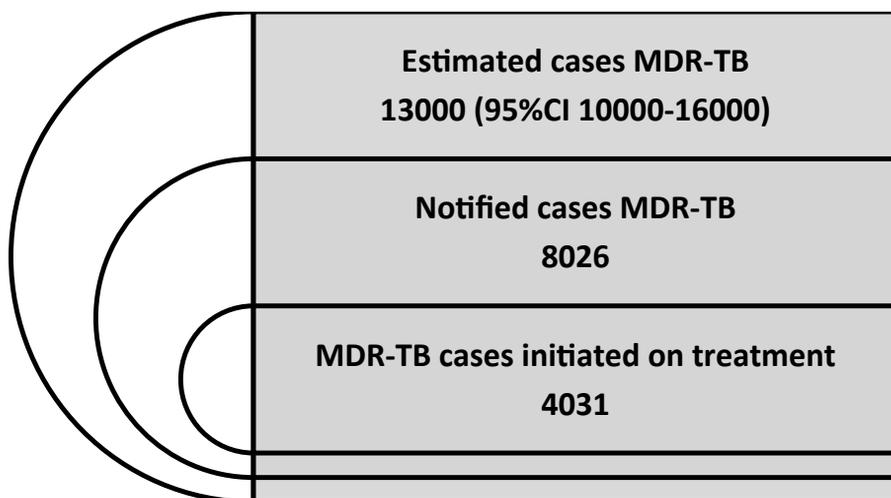


Figure 2.3 Estimated total number of MDR-TB cases in South Africa with notified cases and treated cases, 2008¹⁵

A recent report from a national drug resistance survey in the Kingdom of Swaziland in 2009-2010 has shown much more concerning levels of resistance¹⁶. The proportions of cases with MDR were 7.7% for new smear positive cases and 33.8% for previously treated smear positive cases. This represented substantial escalation from levels documented in their previous national survey in 1995 and are the highest proportions ever documented in Africa.

The Swaziland survey also suggested an association between MDR and HIV infection¹⁶. Prior to this, there was no strong evidence of a specific epidemiological link between HIV infection and MDR-TB in this region¹⁷. So whether HIV infection *per se* increases the risk of drug resistance remains unclear. However, as most TB disease in Southern Africa is HIV-associated, this is also the case with MDR-TB and up to 80% of cases will be HIV infected.

XDR-TB has been reported from several countries in Southern Africa (South Africa, Botswana, Mozambique, Swaziland, and Lesotho)¹². In South Africa between 2007 and 2011 the proportion of MDR isolates that were XDR was 6.2%¹⁴, although there remain epidemiological pockets with much higher XDR prevalence (e.g. uMzinyathi district in KwaZulu-Natal).

2.4. Development of drug resistance

Drug resistance in *M. tuberculosis* occurs through a similar process to HIV drug resistance¹⁸. Spontaneous bacterial chromosomal mutation results in organisms that are naturally resistant to certain drugs. The rate of naturally occurring drug-resistant mutants varies for individual drugs from between 1 in 10⁵ and 10⁹ cell divisions. Killing of susceptible bacilli by anti-TB drugs leads to the selection and preferential growth of resistant strains. The locations of resistance to different drugs in the genome are not linked, so spontaneously occurring multidrug resistance is rare, and rather multidrug resistance arises due to the accumulation of multiple mutations over time.

Another important concept which contributes to TB drug resistance is that of compartmentalisation of bacilli¹⁹. Untreated TB disease is characterised by different populations of *M. tuberculosis* located in different sites with different micro-environments (e.g. pulmonary cavities, caseous lymph nodes etc.). Each of the first-line TB drugs is active against different populations of bacilli, as illustrated in FIGURE 2.4. This compartmentalisation increases the risk of bacilli being exposed to monotherapy and promotes the growth of drug-resistant strains.

Rifampicin	<ul style="list-style-type: none"> •Active against slow-growing/dormant bacilli, including those within macrophages •Critical for sterilising sputum in pulmonary disease
Isoniazid	<ul style="list-style-type: none"> •Bactericidal for rapidly growing bacilli in aerobic environment (e.g. pulmonary cavities) •Critical early in therapy (early bactericidal activity)
Ethambutol	<ul style="list-style-type: none"> •Targeted at metabolically active organisms •No activity against non-replicating bacilli
Pyrazinamide	<ul style="list-style-type: none"> •Active at low pH, kills organisms inside caseous necrotic foci and cavities

Figure 2.4 Preferential targets and sites of action of key first-line antituberculosis drugs

2.5. Diagnosis of TB drug resistance

Drug resistance in *M. tuberculosis* can be determined by phenotypic or genotypic methods. Historically drug susceptibility testing (DST) has used phenotypic methods, whereby the organism is cultured in the presence of a critical drug concentration. Through this method clinical isolates are classified as 'susceptible' or 'resistant'. It is important to note that these definitions are based on the laboratory testing and may or may not accurately predict the clinical response²⁰.

Improved understanding of the molecular mechanisms of drug resistance (see TABLE 2.1) has led to the development of molecular diagnostic tools for the detection of drug resistance. The Genotype MTBDR_{plus} assay is a line probe assay which detects mutations in the *rpoB*, *katG*, and *inhA* genes and thus identifies rifampicin and isoniazid resistance^{21,22}. This test has been recommended for use on smear-positive or culture-positive specimens by the WHO and has been implemented in certain countries, e.g. South Africa²³. Results can theoretically be produced within 24 hours but this technology still requires substantial laboratory infrastructure and technical expertise. A companion assay, the Genotype MTBDR_s assay detects mutations in the *rrs*, *gyrA*, and *embB* genes, respectively conferring resistance to fluoroquinolones, second-line injectable agents, and ethambutol²⁴. This line probe assay (if used as an addition to the MTBDR_{plus}) thus has the potential to identify XDR isolates. It is not yet in routine use but the evidence surrounding the assay is due to be examined by the WHO in 2012.

More recently the Xpert MTB/RIF system has been introduced and has also been recommended for use by the WHO²⁵⁻²⁷. This molecular system uses molecular beacon technology to detect mutations in the *rpoB* gene which confer rifampicin resistance. As rifampicin mono-resistance is relatively rare, this can be considered a reasonable proxy for the detection of MDR-TB. This test can be performed directly on sputum and the result generated in two hours. Given that it only identifies resistance to rifampicin, the detection of resistance should prompt further genotypic or phenotypic DST. A good summary of the development and application of the test can be found elsewhere²⁸. South Africa has embarked on an ambitious plan to scale up this technology within the National Health Laboratory Service. There are also plans to implement the system in Botswana and Swaziland. The current Xpert MTB/RIF diagnostic algorithm in use within South Africa is shown in FIGURE 2.5. FIGURE 2.6 illustrates the genetic target sequences for the Genotype MTBDR_{plus} assay and the Xpert MTB/RIF assay.

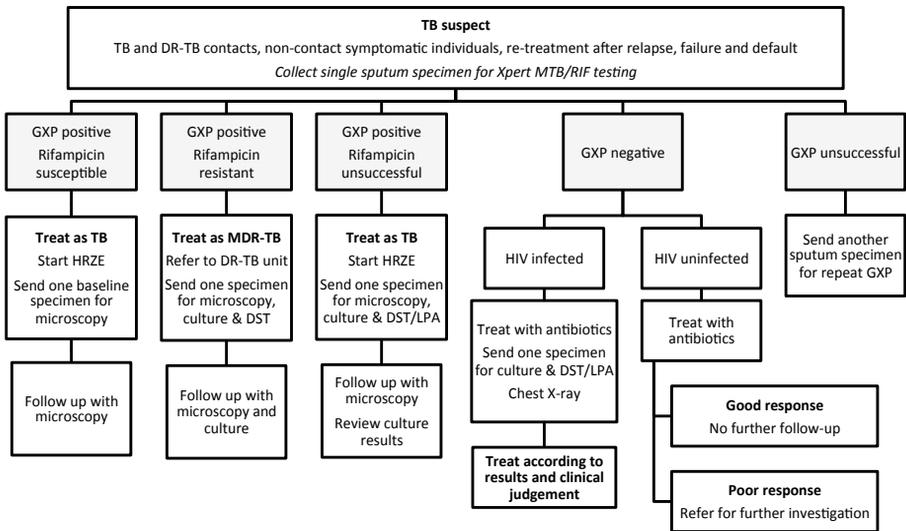
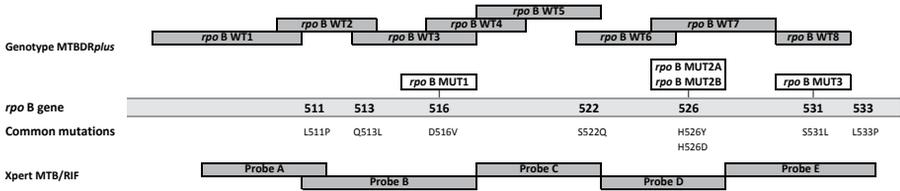
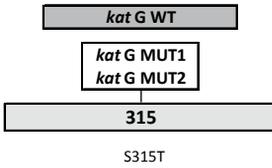


Figure 2.5 Diagnostic algorithm incorporating Xpert MTB/RIF for use in South Africa (adapted from national drug-resistant tuberculosis guidelines³¹)

A



B



C

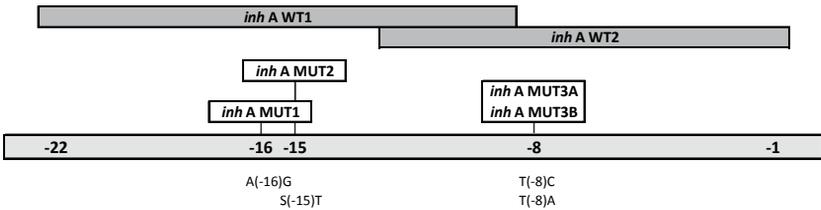


Figure 2.6 Target genes and sequences for the Genotype MTBDRplus and Xpert MTB/RIF assays: *rpoB* gene targeted by both assays (A); *katG* gene targeted by Genotype MTBDRplus (B); *inhA* gene targeted by Genotype MTBDRplus (C)

2.6. Management of drug-resistant TB disease

The principles underlying the programmatic management of drug-resistant TB disease (taken from the latest WHO guidelines) are shown in TABLE 2.2. Further information regarding the programmatic management of MDR-TB can be found elsewhere²⁹⁻³².

TABLE 2.2 *Key principles in programmatic management of MDR-TB (from WHO guidelines³⁰)*

1	Four second-line drugs likely to be effective (including an injectable), as well as pyrazinamide, should be used in the intensive phase
2	A fluoroquinolone should be used (ideally a late-generation fluoroquinolone, e.g. moxifloxacin)
3	Ethionamide should be used
4	The intensive phase should be at least eight months duration
5	The total treatment duration should be at least 20 months
6	A combination of sputum smear microscopy and culture should be used for monitoring patients during treatment
7	All HIV-infected individuals should receive ART, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of anti-TB therapy

These principles guide the formation of standardised treatment regimens, which are used in the public sector in most countries of Southern Africa. An example of a standardised regimen for MDR-TB would be: 8Z-Km-Mfx-Eto-Tzd/16Z-Mfx-Eto-Tzd

An individualised approach would involve specific selection of drug regimen based on previous treatment history and results of genotypic and/or phenotypic DST. The two approaches might be combined, in that a standardised regimen could be commenced on the basis of an initial diagnostic test (e.g. Xpert MTB/RIF) and then the regimen adjusted or optimised on the basis of further DST results.

With regards to the standardised regimen there are a few issues worth further consideration:

1. Which injectable agent should be used?

All three second-line injectable agents (kanamycin, amikacin and capreomycin) have similar efficacy and adverse effect profiles, with ototoxicity and nephrotoxicity being the most important. There is also a high degree of cross-resistance between the three drugs (through mutations in the *rrs* gene) although this might not be complete³³⁻³⁴. It is thought that some kanamycin- and amikacin-resistant strains might retain activity against capreomycin and this is the rationale for kanamycin or amikacin being used for MDR-TB treatment, with capreomycin reserved for use in XDR-TB regimens. Kanamycin is less expensive than amikacin and is currently the preferred agent in South Africa.

2. Which fluoroquinolone should be used?

In southern Africa, ofloxacin has until recently been the fluoroquinolone in use for MDR-TB treatment. However, there is evidence that moxifloxacin has considerably better activity than ofloxacin³⁵. South African guidelines now recommend the use of moxifloxacin in MDR-TB regimens. The extent of cross-class resistance is again not entirely clear, with some evidence to suggest that moxifloxacin retains activity against some ofloxacin-resistant strains. It should be noted that ciprofloxacin should never be used for treatment of MDR-TB.

3. Should other first-line drugs (ethambutol & pyrazinamide) be used?

Phenotypic DST for both ethambutol and pyrazinamide can be complex and interpretation of results can be unreliable. Decisions about whether to include these drugs in an MDR-TB regimen are usually based on the patient's previous exposure to these drugs. However, data from South Africa have demonstrated that probably over half of all MDR-TB isolates have genotypic evidence of resistance to ethambutol³⁶. Similar data have shown around 50% of MDR-TB isolates in the Western Cape region to have phenotypic and/or genotypic resistance to pyrazinamide³⁷. Greater understanding of the genotypic determinants of resistance and more up-to-date surveillance data are required to inform the use of these drugs in MDR-TB treatment regimens. The important point is that, even if these drugs are included in a treatment regimen, neither should be considered one of the four active drugs.

2.7. Models of care for drug-resistant TB

Historically management of drug-resistant TB has been centralised with care delivered through specialist hospitals at provincial or national level. Patients were usually managed as inpatients at least for the intensive phase (i.e. first six months of treatment). The huge burden of disease has by necessity forced certain countries (predominantly South Africa) to scale-up decentralised models of care as the provincial referral centres have not had the capacity to manage the caseload. The other driving force for the decentralisation is the recognition that centralised models are not responsive to the needs of patients and that decentralised models potentially offer more 'patient-centred care'. There is some preliminary evidence from South Africa that decentralised models of care can shorten the time to treatment initiation and might also improve early treatment outcomes compared to the traditional centralised model^{38,39}. There is a need for longer-term data on treatment outcomes and on retention in care as these decentralised services scale up. In South Africa, there is now a published policy framework to guide the scale up of decentralised drug-resistant TB services⁴⁰.

2.8. References

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