

# Treatment of drug-resistant tuberculosis

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**Clinical question:** What is the best approach to the treatment of drug-resistant tuberculosis (TB)?

**Results:** Evidence-based treatment of drug-susceptible TB is the best means of preventing the development of drug-resistant disease. Suspecting the possibility of drug-resistant TB, and prompt detection of all forms of drug-resistant TB, not only multidrug-resistant and extensively drug-resistant TB, should be part of the algorithm for diagnosis and management of all patients with active TB.

**Implementation:** Treatment of all forms of drug-resistant TB must be tailored to the specific form of resistance with appropriate and effective drug regimens.

**Keywords:** drug-resistant tuberculosis, MDR-TB, treatment

## Introduction

Tuberculosis (TB) is a global pandemic, with 9.4 million incident cases occurring in 2009 and 1.7 million deaths attributed to the disease.<sup>1</sup> In addition to the worrisome reality that the total number of cases globally is still increasing (although incidence rates are decreasing slightly), disease due to strains of *Mycobacterium tuberculosis* (MTB) that are resistant to treatment by first-line drugs is a serious threat to global TB control.

It is estimated that 17% of all new TB cases worldwide (population-weighted proportion) harbor some form of drug resistance.<sup>2</sup> The poorer outcomes and complexities of treatment associated with drug-resistant disease make it necessary to promptly recognize, and adequately treat all forms of drug-resistant disease. The objective of this review is to summarize the pathogenesis of drug-resistant TB, and use this understanding of pathogenesis, along with the best available published evidence to outline the key principles of prevention and treatment of drug-resistant TB.

## Epidemiology and impact of drug-resistant TB

The World Health Organization (WHO) has estimated that 17% of all newly diagnosed patients with active TB have disease caused by drug-resistant strains. Of all TB patients, 14.1% have either mono- or poly-drug resistance, over half of whom (7.4% of the global total) are resistant to isoniazid alone. Such forms of mono- and poly-resistant strains are seen in higher proportions in countries with high rates of MDR-TB.<sup>3</sup> An estimated 2.9% of all new TB cases globally are multi-drug resistant (MDR-TB, defined as resistance to both isoniazid and rifampicin, the two most important first-line drugs). Less than 1% of new cases globally are reported to be extensively drug-resistant TB (XDR-TB), defined

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as MDR-TB plus resistance to a second-line injectable drug and a fluoroquinolone). In twelve countries, 6% or more of new cases have MDR-TB, while 58 countries to date have reported at least one case of XDR-TB.<sup>2</sup>

Outcomes of treatment of drug-resistant TB are worse than drug-susceptible TB (DS-TB). The most extreme is XDR-TB – in the first reported outbreak of XDR-TB among HIV-infected individuals, all but one of 53 XDR-TB patients died of the disease, with a median survival of 16 days from the time the first sputum specimen was collected.<sup>4</sup> However, a subsequent study from Peru reported that 29 of 48 (60%) HIV-uninfected patients with XDR-TB were treated successfully.<sup>5</sup>

Outcomes of treatment of MDR-TB are somewhat better. Three systematic reviews estimated pooled success treatment rates of only 60%–70%, with failure rates of 10%–11%, mortality of 10%–15%, and default rates of up to 20%.<sup>6–8</sup> Treatment of MDR-TB involves the use of second-line drugs that are less efficacious than first-line drugs, more expensive, and have more adverse effects, making tolerance and treatment adherence challenging. The cost of treatment from drugs alone is estimated to be 50–200 times higher for MDR-TB patients, compared with treatment of patients with drug-susceptible TB.<sup>9</sup> An estimated 150,000 deaths were caused by MDR-TB in 2008, the majority because they were not treated with second-line drugs.<sup>9</sup>

The remaining and much more common forms of drug-resistant TB have significantly worse outcomes than DS-TB, although cure rates with existing regimens are potentially higher than for MDR or XDR. A systematic review of studies of patients with strains that were isoniazid-resistant found significantly higher rates of failure, relapse, and acquired drug-resistance than in patients infected with strains that were susceptible to all drugs when treated with standardized regimens.<sup>3</sup> Pooled failure and relapse rates were 10%–15% higher than among new cases with DS-TB.<sup>10</sup> Outcomes were even worse among previously treated patients with isoniazid mono-resistance, in whom the combined failure and relapse rates ranged from 29% to 70% when treated with the WHO recommended standardized re-treatment regimen.<sup>10</sup> A study of intermittent regimens among HIV-infected patients with TB found isoniazid mono-resistance to be the main risk factor for acquired rifamycin resistance.<sup>11</sup>

## Pathogenesis of drug resistance – how does drug resistance develop?

In every  $10^6$  to  $10^8$  replications, wild strains of *MTB* undergo spontaneous mutations that confer resistance to a single drug;

the average number of such spontaneous mutations to anti-TB drugs is shown in Table 1.<sup>12</sup> When treated with a single drug, the population of TB bacilli initially shrinks due to the killing of susceptible organisms in the population, often rendering a person smear-negative (as a result of fewer organisms being present). However, the organisms that survive the initial phase are the drug-resistant mutants, and the proliferation of these mutants eventually causes the entire population of bacilli to be replaced by drug-resistant forms that continue to proliferate until they are numerous enough to cause recurrence of symptoms, and smear positivity; this is termed “the fall and rise phenomenon”.<sup>13</sup>

If treated with a single drug, and the bacillary load of the organisms exceeds  $10^6$ , then emergence of strains that are resistant to that drug is almost certain. If the bacillary load exceeds  $10^8$  then resistance is likely to develop if only two drugs are used. Bacillary loads exceed  $10^6$  with tuberculous infiltrates alone (when sputum direct smears are negative although cultures are positive), and exceed  $10^8$  when cavities are present in patients with TB, at which time sputum direct smears are usually positive.<sup>14,15</sup> One of the aims of modern anti-TB therapy is to prevent drug resistant mutants from proliferating. This is best accomplished by including at least three likely effective anti-tuberculous agents in the initial treatment regimen, as this will reduce the probability of emergence of drug resistance to  $10^{-18}$  or lower.

During the initial phase of treatment the few mutants with spontaneous resistance to one drug will be killed more slowly than the “wild type” bacilli that are susceptible to all drugs. Hence during the first months of therapy these more resistant bacilli will survive longer. If therapy is interrupted early, through default, then these drug-resistant mutants will proliferate, increasing the proportion of drug-resistant forms, until this proportion becomes clinically significant. Low drug levels, either from malabsorption (as occurs in HIV-infected patients) or inadequate dosages of medications, will have the same effect. In the presence of isoniazid mono-resistance, for example, the use of the recommended two-drug therapy in the continuation phase of treatment is effectively rifampicin

**Table 1** Rates of spontaneous mutations conferring resistance to anti-TB drugs<sup>12,27</sup>

Drug	Average mutation rate
Isoniazid	$2.56 \times 10^{-8}$
Rifampicin	$2.25 \times 10^{-10}$
Ethambutol	$1 \times 10^{-7}$
Streptomycin	$2.95 \times 10^{-8}$
Pyrazinamide	$1 \times 10^{-3}$

monotherapy; this can explain the acquired rifamycin resistance observed in one recent trial with such patients,<sup>11</sup> and the poor outcomes observed when isoniazid-resistant patients are treated with standardized regimens.<sup>16</sup>

In summary, during treatment three possible mechanisms can result in the selection of drug-resistant mutant strains: treatment with an inadequate number of effective drugs, sub-therapeutic dosing or absorption, or treatment interruption. Patient consumption of all doses of an appropriate drug regimen with the correct dosages is essential to prevent resistance. The value of evidence-based adequate drug regimens cannot be over-emphasized; unfortunately, these seem to be flouted in countries where drug regulatory systems are lax, and private physicians and pharmacies are allowed to prescribe drugs in an unregulated manner. For example, a study of the prescriptions for TB among private practitioners in Mumbai, India, found that 106 practitioners prescribed 63 different regimens, only six of which were judged adequate.<sup>17</sup> A study found that of the 20 countries with the highest MDR-TB prevalence, eleven had no adequate policies for sales and distribution of TB drugs. Regulation of rifampicin sales was also negatively correlated with the prevalence of MDR-TB.<sup>18</sup> Controlling TB drugs at the national level and preventing their misuse, therefore, would be a key component to ensuring that TB patients receive appropriate treatment.

## When should drug-resistant TB be suspected, and how should it be diagnosed?

The algorithm for the diagnosis of drug-resistant TB is founded on an understanding of the profile of TB patients who have a higher probability of harboring drug-resistant strains. This profile holds true for all forms of the disease, including paucibacillary (smear negative) forms.

Patients at risk of drug-resistant TB fall into three major groups: contacts of patients with drug-resistant TB, previously treated, and those who are failing therapy. Close contacts of patients with drug-resistant TB are more likely to have been infected with a resistant strain, and if they have active TB should be presumed to harbor a drug-resistant strain.<sup>19</sup> Patients who have received TB treatment in the past include those who relapsed (have TB disease again after being declared “cured” in the past) and those who defaulted (did not complete a course of TB treatment as recommended in the past). Close to one-third of all patients who default or relapse will have MDR-TB strains.<sup>16</sup> It is therefore vital to obtain an accurate history of prior TB treatment as this is a very strong risk factor for drug-resistant TB.<sup>16</sup> Up to 90% of all patients who fail treatment,

defined as a positive AFB sputum smear or culture after 5 months of therapy, will have MDR-TB strains.<sup>16</sup> Given this, patients who remain smear positive after 3 months of treatment should be investigated for possible drug-resistant TB.<sup>20</sup>

The diagnosis of drug-resistant TB is made by performing drug-susceptibility testing (DST) of the strain of TB obtained from the patient. Patients who are at risk of drug-resistant TB based on the profiles mentioned above should be subjected to DST testing. Testing can be performed on traditional solid media such as Lowenstein-Jensen media, which is relatively inexpensive but requires 4–8 weeks for a result. DST using liquid media such as MGIT (Mycobacteria Growth Indicator Tube) provides results in 2–4 weeks, but is more expensive. Molecular methods, such as Xpert-Rif, can provide results within hours, but are the most expensive of all the currently available tests. A detailed description of these methods is beyond the scope of this article, but can be found at <http://www.tbvidence.org>.

## Principles of treatment of TB – how to prevent drug resistance

The broad objectives of anti-TB treatment are: (1) rapid reduction in bacillary load to reduce morbidity and mortality, and stop transmission, (2) prevent the emergence of drug-resistant mutant strains, and (3) prevent relapse of disease.

To achieve objective 1, potent bactericidal drugs such as isoniazid, especially in the first week, and rifampicin are the most useful. To achieve the second objective, multiple drugs with proven (by DST) or likely (never previously used) efficacy are used, to prevent the selection of drug-resistant mutants as explained earlier. To achieve the third objective, treatment is prescribed for a sufficiently long duration, with monitoring of adherence to treatment, to eliminate residual surviving organisms that are responsible for disease relapse. The length of treatment with rifampicin plays an important role in achieving this third objective.<sup>21</sup>

Recommendations for the dosages, duration, and combinations of drugs for treatment of drug-susceptible TB are based on sound evidence-based principles derived from multiple randomized trials.<sup>21</sup> Adherence to authoritative guidelines for treatment<sup>22</sup> and ensuring that all doses are taken correctly is unarguably the most effective means of preventing drug resistance.

## Treatment of suspected drug-resistant TB

The “standardized” approach to treatment of suspected resistant TB is to design a regimen based on local drug

surveillance data. The advantage of such a standardized approach is that it prevents major errors in number, dosages, and duration of TB drugs.

The “empiric” approach, in contrast, takes into account the patient’s drug history, assuming the patient to be potentially resistant to the drugs that have been used in the past, thus tailoring treatment to the individual, at the risk of not using some of the drugs that the patient may still be susceptible to. This may then be modified if and when DST results are available.

The “individualized” treatment modifies the standardized or the empiric treatment to match treatment to individual drug susceptibility patterns once the results of a DST of the sputum culture are available. The choice of approach is dependent on available resources, but it is recommended that all patients have a DST immediately once resistance is suspected (based on the criteria listed above), and that empiric treatment for drug-resistant TB is commenced while awaiting the results of the DST.<sup>23</sup>

In the absence of a known contact with MDR-TB and when isoniazid mono-resistance is not suspected (based on population estimates of prevalence less than 4%), patients with active TB who have never before been treated should receive 6 months of rifampicin (R) and isoniazid (H), with pyrazinamide (Z) also prescribed in the initial 2 months of treatment (2HRZ/4HR).

Patients with active TB who had contact with a patient with documented drug-resistant TB should be started on treatment tailored to the susceptibility pattern of the source case, while awaiting the results of a DST on the strain of MTB isolated from the patient.

In new cases, but in areas where the prevalence of isoniazid resistance exceeds 10%, we recommend, treatment with an intensive phase of 2 months consisting of four drugs (H, R, Z, and Ethambutol (E)), while the continuation phase should include ethambutol throughout, in addition to isoniazid and rifampicin, if DST are not available.<sup>1</sup> If DST are available then initial empiric therapy should include HRZE until DST results are available.

In cases of different forms of suspected drug-resistant TB, the normal regimen should be commenced, which should then be individualized once results of a DST are available. In view of the increased number of drugs, the prolonged duration of treatment and the need to be aware of possible interactions and adverse drug reactions of second-line drugs, we recommend the referral of patients with drug-resistant TB to TB specialists for treatment.

## Treatment of confirmed drug-resistant TB

A great deal of writing about the management of drug-resistant TB has focused on the treatment of MDR-TB and more recently, XDR-TB. While these forms are known to have much worse outcomes than drug-susceptible TB,<sup>3</sup> failure to adequately treat other forms of mono- and poly-resistant TB would be highly imprudent. Failure to treat patients with these patterns of resistance with adequate regimens will lead to the development of MDR- and XDR-TB, with disastrous immediate consequences for the individual patients, and for TB control programs in the long term.<sup>24</sup>

Five broad groups of drugs used for the treatment of drug-resistant TB (in hierarchical order of importance and preference while designing a regimen), are listed in Table 4. The dosages of the most important, recommended second-line drugs are detailed in Table 2.<sup>23</sup>

### Isoniazid mono-resistance

The standard recommendation is 2 months Rifampin, Pyrazinamide plus Ethambutol, followed by 8 months Rifampin plus Ethambutol 2RZE+8RE. However this is of unproven efficacy. Given the evidence that treatment with standard regimens for new or previously treated cases is ineffective, as reviewed earlier, we do not recommend this. On the other hand moxifloxacin has been found in two studies to have equivalent efficacy as isoniazid when used along with RZE in TB patients with drug-susceptible strains.<sup>25,26</sup> Therefore we suggest, a substitution of isoniazid with a fluoroquinolone throughout treatment for isoniazid mono-resistant active TB (Table 3).

### Poly-drug resistance and other forms of mono-resistance

The many possible forms, each with specific treatment recommendations, are summarized in Table 3. Note that many authorities recommend the same treatment for mono-Rif resistance as for MDR-TB.

### MDR-TB

The treatment regimen for confirmed MDR-TB is tailored to the DST profile if available. However while awaiting DST, or if DST are not available, treatment principles include the initial use of at least four drugs that the patient should be susceptible to (likely effective), and including an injectable for at least 7 months, and at least three likely effective drugs in the continuation phase for a total of 18–21 months. Ideally,

**Table 2** Dosage, action and adverse reactions of first-line and selected second-line anti-TB drugs

Drug	Daily dose and range (mg/kg body weight), maximum dose (mg)	Role in the treatment strategy	Adverse reactions
Rifampicin	10 (8–12), 600	<ul style="list-style-type: none"> <li>• Most important anti-TB drug</li> <li>• Bactericidal and sterilizing, rapidly rendering the patient non-infective</li> <li>• Allows shortening of therapy to half</li> </ul>	<ul style="list-style-type: none"> <li>• Hepatotoxicity</li> <li>• Rash</li> <li>• Hematologic</li> </ul>
Isoniazid	5 (4–6), 300	<ul style="list-style-type: none"> <li>• Bactericidal</li> <li>• Potent early bactericidal activity</li> </ul>	<ul style="list-style-type: none"> <li>• Hepatotoxicity</li> <li>• Rash</li> <li>• Neuropathy</li> <li>• Lupus-like reaction</li> <li>• Anemia</li> </ul>
Pyrazinamide	25 (20–30), 2000	<ul style="list-style-type: none"> <li>• Bactericidal early effect</li> <li>• Allows shortening of therapy by 3 months in DS-TB</li> </ul>	<ul style="list-style-type: none"> <li>• Hepatotoxicity</li> <li>• Rash</li> <li>• Arthralgias</li> </ul>
Ethambutol	15 (15–20), 1600	<ul style="list-style-type: none"> <li>• Bacteriostatic</li> <li>• The least effective drug, but protects against resistance</li> </ul>	<ul style="list-style-type: none"> <li>• Optic neuritis (can cause blindness)</li> <li>• Rash</li> </ul>
Streptomycin	15, 1000	<ul style="list-style-type: none"> <li>• Bactericidal</li> </ul>	<ul style="list-style-type: none"> <li>• Nephrotoxicity</li> <li>• Vestibular toxicity</li> <li>• Ototoxicity</li> </ul>
Kanamycin	15, 1000	<ul style="list-style-type: none"> <li>• Bactericidal</li> </ul>	<ul style="list-style-type: none"> <li>• Nephrotoxicity</li> <li>• Vestibular toxicity</li> <li>• Ototoxicity</li> </ul>
Levofloxacin	750–1000 mg/day	<ul style="list-style-type: none"> <li>• Strong anti-TB activity</li> </ul>	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Tremulousness, insomnia</li> <li>• Arthralgias</li> <li>• Rare QT<sub>c</sub> prolongation, tendon rupture</li> </ul>
Ethionamide	15 (15–20), 1000 frequently divided	<ul style="list-style-type: none"> <li>• Bacteriostatic</li> </ul>	<ul style="list-style-type: none"> <li>• Gastrointestinal upset and nausea</li> <li>• Hepatotoxicity</li> <li>• Reversible hypothyroidism</li> </ul>

**Abbreviation:** DS-TB, drug-susceptible TB.

**Table 3** Regimens for the treatment of mono-resistant and poly-resistant strains<sup>28</sup>

Pattern of drug resistance	Suggested regimen	Minimum duration of treatment in months
H	2RZE and FQ followed by 4–7 R and FQ (FQ = 400 mg moxifloxacin or 750–1000 mg levofloxacin substituted for H in the standard treatment regimen)	6–9
R	2HZE and FQ followed by 10–16 HE and FQ ± injectable for the initial 6 months	12–18
H and Z	RE and FQ	9–12 (longer if extensive disease)
H and E	RZ and FQ	9–12 (longer if extensive disease)
R and E (±S)	HZ and FQ, plus injectable for at least the first 2–3 months (6 months if extensive disease)	18
R and Z (±S)	HE and FQ, plus injectable for at least the first 2–3 months (6 months if extensive disease)	18
H, E, Z (±S)	R and FQ, plus an oral second-line agent, plus injectable for at least the first 2–3 months (6 months if extensive disease)	18

**Abbreviations:** H, isoniazid; R, rifampicin; E, ethambutol; Z, pyrazinamide; S, streptomycin; FQ, fluoroquinolone.



**Table 4** Grouping of second-line anti-TB drugs for treatment of multidrug-resistant TB

Group	Drugs
Group 1: First-line oral drugs	Pyrazinamide Ethambutol Rifabutin
Group 2: Injectable drugs	Kanamycin Amikacin Capreomycin Streptomycin
Group 3: Fluoroquinolones	Levofloxacin Moxifloxacin Ofloxacin
Group 4: Oral bacteriostatic second-line drugs	Para-aminosalicylic acid Cycloserine Terizidone Ethionamide Prothionamide
Group 5: Drugs with an unclear role in the treatment of drug-resistant TB	Clofazimine Linezolid Amoxicillin/clavulanate Thioacetazone Imipenem/cilastatin High-dose isoniazid Clarithromycin

this should include all drugs from Group 1 (pyrazinamide and ethambutol) to which the patient is susceptible, a second-line injectable (from Group 2), a later generation quinolone (moxifloxacin or levofloxacin – from Group 3), and additional drugs from groups 4 and 5 to complete an adequate regimen. Ethionamide/prothionamide appear to be the most effective of the Group 4 drugs. The injectable agent is prescribed for a minimum of 7 months, and ideally for at least 4 months beyond when the patient first becomes smear- or culture-negative.<sup>23</sup>

## XDR-TB

The principles used for treatment, based on the study from Peru, which has reported the highest success rates to date, are similar to those used for the treatment of MDR-TB, with oral agents prescribed for at least 18 months and injectable drugs prescribed for at least 8 months beyond culture conversion. In the Peru cohort, 14.6% of all patients underwent lung resection surgery as an adjunct to chemotherapy. Only eleven of the 48 patients needed hospitalization during treatment, highlighting the possibility of successful outpatient treatment of XDR-TB.<sup>5</sup>

## Conclusion

The occurrence of rare, spontaneous mutations during replication of the TB bacillus is a natural phenomenon, but the preferential selection and propagation of such resistant

mutants is man-made, and largely preventable. Regimens for drug-susceptible TB have a strong evidence base and, when employed in the right dosages for the right duration with close monitoring of adherence, lead to high cure rates without the development of drug-resistant strains. Getting treatment right the first time should therefore be the primary focus of TB control programs worldwide.

Detection of all forms of drug-resistance, not only MDR- and XDR-TB, should be an integral part of the diagnosis and management of all patients with active TB. Treatment of all forms of drug-resistant TB must be tailored to the specific form of resistance with appropriate and effective drug regimens.

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