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SERIES "UPDATE ON TUBERCULOSIS"
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Treatment of tuberculosis: update 2010

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ABSTRACT: Currently, the standard short-course chemotherapy for tuberculosis comprises a 6-month regimen, with a four-drug intensive phase and a two-drug continuation phase. Alternative chemotherapy using more costly and toxic drugs, often for prolonged durations generally >18 months, is required for multidrug-resistant and extensively drug-resistant tuberculosis. Directly observed treatment, as part of a holistic care programme, is a cost-effective strategy to ensure high treatment success and curtail development of drug resistance in tuberculosis. New antituberculosis drugs are urgently needed to improve the present standard short-course and alternative chemotherapies, by shortening administration durations and increasing cure rates, through the greater potency of these agents. At the same time, the role of adjunctive surgery for drug-resistant tuberculosis has to be better defined. Immunotherapy might improve treatment outcomes of both drug-susceptible and -resistant tuberculosis, and warrants further exploration.

KEYWORDS: Review, tuberculosis, treatment

In 2008, 11.5 million people were estimated to be living with tuberculosis, with 9.4 million of them having incident disease. Among the 1.9 million people who died of tuberculosis, 0.5 million were seropositive for HIV [1]. While the present chemotherapy for tuberculosis is highly efficacious, it has the disadvantages of being lengthy and complex, and does not live up to the expectation of adequately controlling the current global tuberculosis situation. In 2008, an estimated 390,000–510,000 cases of multidrug-resistant (MDR) tuberculosis with bacillary resistance to at least isoniazid (H) and rifampicin (R) are estimated to emerge every year worldwide, with China and India together accounting for ~50% of this global burden. In 2008, MDR tuberculosis caused an estimated 150,000 deaths [2]. Recently emerging extensively drug-resistant (XDR) tuberculosis is defined as MDR tuberculosis with additional bacillary resistance to any fluoroquinolone and one or more of the three (second-line) injectable drugs: amikacin, capreomycin and kanamycin. Approximately 5.4% of MDR tuberculosis reported worldwide could be categorised as XDR tuberculosis, with the proportion exceeding 10% in some countries [2]. This article examines the current status and future prospects of treatment of tuberculosis. Where appropriate, evidence levels for the recommended treatment regimens and modalities are given in accordance with the grading system of the Scottish Intercollegiate Guidelines Network (see Appendix) [3].

Before discussing recommended drug regimens for treating of pulmonary tuberculosis, an understanding of basic mycobacteriology and antituberculosis drug action would be beneficial.

SCIENTIFIC BASIS OF SHORT-COURSE CHEMOTHERAPY

Mycobacterium tuberculosis, the causative organism of tuberculosis, is a slow-growing bacterium that can also enter a phase of dormancy, which appears to be drug-refractory. Four hypothetical populations of organisms [4] may exist in a patient with tuberculosis: 1) actively growing organisms, usually present in abundance (extracellularly) within aerated cavities; 2) slow, intermittently growing organisms in an unstable part of the lesion; 3) organisms surviving under microaerobic conditions in a low environmental pH, either in inflammatory lesions or within phagolysosomes of macrophages; and 4) completely dormant organisms surviving under anaerobic conditions.

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The three major actions of antituberculosis drugs [5] are: 1) bactericidal action, defined as their ability to kill actively growing bacilli rapidly, *e.g.* isoniazid, and to a lesser extent, rifampicin and streptomycin (S); 2) sterilising action, defined as their capacity to kill the semi-dormant organisms, *e.g.* rifampicin and pyrazinamide (Z); 3) prevention of emergence of bacillary resistance to drugs, *e.g.* isoniazid and rifampicin; less so for streptomycin, ethambutol (E) and pyrazinamide; least for thiacetazone and *para*-aminosalicylic acid.

CHEMOTHERAPY OF PULMONARY TUBERCULOSIS

Short-course chemotherapy regimens

Based on a number of clinical trials performed previously, much knowledge has accumulated regarding chemotherapy regimens for new cases of smear-positive pulmonary tuberculosis [6–15]. The shortest duration of treatment required is, at present, 6 months (grade A). The standard regimen today, as categorically recommended by the World Health Organization (WHO) and International Union Against Tuberculosis and Lung Disease (IUATLD) [16], comprises the combination of HRZE for 2 months, followed by HR for a further 4 months. The aminoglycoside streptomycin is not generally recommended as a fourth drug in the intensive phase, largely because of its higher resistance rate than that of ethambutol [17], and its requirement for the parenteral route of administration. However, in rare occasions when ethambutol use is contraindicated, the streptomycin may be considered. Dosages for the conventional first-line antituberculosis drugs are well established, and can be found in standard references [16, 18].

Although an 8-month regimen consisting of 2 months of SHRZ, followed by 6 months of isoniazid and thiacetazone, combined with hospitalisation in the first 2 months, has previously been shown to be effective in controlled clinical trials and programme settings in Africa [11], a randomised study initiated by IUATLD revealed that the 8-month regimen 2HRZE/6HE was significantly inferior to the 6-month regimen 2HRZE/4HR [19]. A systematic review has also shown that regimens utilising rifampicin only for the first 1–2 months had significantly higher rates of failure, relapse and acquired drug resistance compared with regimens that used rifampicin for 6 months [20]. The WHO currently recommends phasing out of the 8-month regimen [16]. Thus, short-course antituberculosis chemotherapy regimen with both rifampicin and pyrazinamide should contain 6 months, rather than 2 months, of rifampicin for better efficacy (grade A).

A regimen without pyrazinamide in the initial intensive phase must be given for >6 months (grade A). Such a regimen based on isoniazid and rifampicin [13–15] is only good for pansusceptible tuberculosis with limited bacillary load, and has to be given for 9 months (namely 2HRE/7HR or 9HR). This 9-month regimen is usually not recommended for patients in countries with high rates of isoniazid-resistant tuberculosis, except those who cannot tolerate pyrazinamide.

The administration of pyrazinamide beyond 2 months has not been shown to offer any advantage on treatment outcome (grade A) [21, 22]. Also, in cohort and case–control analyses, from ⩾12 weeks after starting treatment, the estimated risk of hepatotoxicity was 2.6% for regimens incorporating pyrazinamide, isoniazid and/or rifampicin and 0.8% for standard regimens containing isoniaizid and rifampicin. Thus, adding pyrazinamide to isoniazid and rifampicin increases the risk of hepatotoxicity appreciably [23].

For individual cases with extensive disease and slow sputum bacteriological conversion, administration of pyrazinamide with or without ethambutol beyond 2 months may seem acceptable. This prolongation of intensive phase is not currently supported by WHO [16]. However, WHO has recently raised the possible advantage of using rifampicin, isoniazid and ethambutol rather than rifampicin and isoniazid in the continuation phase of treatment of tuberculosis in populations with known or suspected high levels of bacillary resistance to isoniazid [16]. Initial cavitation and positive sputum culture after 2 months of treatment have been found to be associated with increased risk of failure or relapse, and possibly justify prolongation of the continuation phase of antituberculosis therapy to give a total duration of 9 months [24] (grade B).

Intermittent regimens comprising two drugs in the continuation phase, following an intensive phase of four drugs given on a daily basis, have been proven to be highly efficacious ($2HRZS/4H_3R_3$ or $2HRZS/4H_2R_2$) (grade A) [7, 10]. WHO does not generally recommend twice-weekly regimens, because of the higher risk of treatment failure when missing doses occur [16]. Intermittent short-course regimens administered three times weekly throughout have been shown to have largely equivalent efficacy to daily regimens [8]. A recent nested case–control study raised concerns regarding the efficacy of three-times-weekly 6-month regimens in preventing disease relapse in the presence of cavitation [25]. The systematic review mentioned earlier [20] did not show any significant difference in failure or relapse with daily or intermittent scheduling of treatment administration, apart from insufficient published evidence for the efficacy of twice-weekly rifampicin administration throughout therapy. However, major confounding factors, such as cavitation and 2-month culture status, might be heterogeneous across the included studies and not adequately controlled for in that systematic review. Furthermore, rates of acquired drug resistance among the failures and relapses have been shown to be higher with three-times-weekly therapy [20]. Dosing schedules in the first 9 weeks did not appear to have impact on the risk of hepatotoxicity in another case–control study [26]. Logistic regression analysis showed that sex was nonsignificant but ageing increased the odds of hepatitis, the risk of which rose from 2.6% to 4.1% as age exceeded 49 yrs.

WHO currently recommends the use of daily dosing during both the intensive and continuation phase as the most optimal approach (table 1).

HIV-infected patients who received 6-month rifampicin- or rifabutin-based regimens were shown to have a higher relapse rate than those on longer therapy in an early clinical trial [27] and a more recent treatment cohort [28]. Possibly because of the poor prognosis associated with the underlying HIV infection before the availability of antiretroviral therapy, the lower relapse rate did not translate into improved survival in the former trial [27]. WHO currently recommends that tuberculosis patients who are living with HIV should receive

TABLE 1 Recommended dosing frequency for standard 6-month regimen

Dosing frequency: intensive phase	Dosing frequency: continuation phase	Comments
Daily	Daily	Optimal
Daily	3 times per week	Acceptable alternative for any new tuberculosis patient receiving directly observed therapy
3 times per week	3 times per week	Acceptable alternative provided that the patient is receiving directly observed therapy and is not living with HIV or living in an HIV-prevalent setting

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at least the same duration of treatment as HIV-negative patients. Increased risk of treatment failure and acquired rifamycin resistance have also been shown to be associated with intermittent regimens among HIV-infected patients [29–31]. WHO currently recommends that HIV-positive patients with tuberculosis and all tuberculosis patients living in HIV-prevalent settings should receive daily treatment, at least during the intensive phase [16].

In many countries, nearly 50% of patients are diagnosed as having active pulmonary tuberculosis on clinical and radiographic grounds, without immediate bacteriological confirmation. In the two smear-negative studies conducted in Hong Kong, China it was found that with 2 and 3 months of daily HRZS treatment, the relapse rates were 32% and 13%, respectively, for culture-positive patients [32], but the rates were much lower with 4-month treatment (2% for drug-susceptible tuberculosis and 8% for isoniazid- and streptomycin-resistant tuberculosis) [33].

Thus, it appears that $\geqslant$4 months of treatment is required for smear-negative pulmonary tuberculosis in non-HIV-infected patients (grade C). WHO currently recommends the use of a 6-month regimen of daily HRZE for 2 months followed by daily or three-times-weekly HR for a further 4 months in the treatment of new smear-negative pulmonary tuberculosis patients [16].

The relapse rates during the 6–30 months following the end of the standard 6-month short-course chemotherapy regimen are generally <5% [6–10]. 78% of relapses occurred within 6 months of stopping treatment, and 91% within 12 months [34].

Retreatment drug regimens

For treatment of smear-positive relapse cases of pulmonary tuberculosis, as well as retreatment after interruption, an 8-month regimen has been recommended by WHO and the IUATLD, namely 2HRZES/1HRZE/5HRE (grade D) [16]. With the increasing availability of rapid tests for bacillary drug susceptibilities, such as line probe assays, it would be possible to modify this approach according to the results, particularly in areas with high prevalence of MDR and XDR tuberculosis [16]. Using conventional drug susceptibility testing, it might be necessary to start an empirical retreatment regimen active against MDR disease when the levels of MDR tuberculosis are high in different patient registration groups in the geographical area (grade D). Patients who have failed two rifampicin-containing regimens, the initial and retreatment regimens, are very likely to have MDR tuberculosis. These updated recommendations are now incorporated in the current WHO guidelines (table 2) [16].

Directly observed treatment, short-course

Directly observed treatment (DOT) was shown to be highly efficacious in ensuring patient adherence by experience gained in Chennai (then Madras), India and Hong Kong many decades ago. In 1993, WHO officially announced the new global strategy for tuberculosis control known as directly observed treatment, short-course (DOTS) that implements the 6-month short-course regimen in a programmatic setting [35, 36]. The DOTS strategy has five key components, which include: 1) a network of trained healthcare or community workers to administer DOT; 2) properly equipped laboratories

TABLE 2 Suggested antituberculosis retreatment regimens for previously treated patients

DST	Likelihood of MDR-TB
Routinely available	High (failure patients)
	Medium/low (relapse/default patients)
Rapid molecular tests	DST results available in 1–2 days to confirm or exclude MDR-TB to guide treatment regimen used
Conventional phenotypic tests	While awaiting DST results, empirical MDR-TB regimen (to be modified once DST results are available)[#]
	While awaiting DST results, 2HRZES/HRZE/5HRE (to be modified once DST results are available)[#]

DST: drug susceptibility testing; MDR-TB: multidrug-resistant tuberculosis. [#]: standardised/individualised regimen if MDR-TB is confirmed. Reproduced and modified from [16] with permission from the publisher.

with trained personnel to perform sputum microscopy for diagnosing tuberculosis; 3) a reliable supply of high-quality drugs (preferably at no cost to patients); 4) an accurate record-keeping and cohort analysis system for monitoring case-finding, treatment and outcomes; and 5) sustained political commitment and funding. An effectively functioning tuberculosis control programme is clearly essential for good patient outcome [36]. Although some patient characteristics, such as homelessness, alcohol or substance abuse, behavioural problems, mental retardation, and lack of social or family support, are more commonly associated with nonadherence to therapy, it is often difficult to identify poorly adherent patients because the underlying reasons for such behaviour are not only multifaceted and complex, but range from characteristics of the individual patients to qualities of the societal and economic environment [37]. Although a Cochrane database systematic review concluded that the results of randomised controlled trials conducted in low-, middle- and high-income countries did not provide assurance that DOT, compared with self-administered treatment, could impart quantitatively important effects on cure or treatment completion in tuberculosis patient [38], the merit of reduction of acquired drug resistance with DOT was not addressed [39]. The DOTS strategy is more than DOT alone: it should be viewed as a comprehensive service, or an integral part thereof, which includes enablers, incentives, education and holistic care that are conducive to the success of the treatment programme. In a cluster randomised controlled trial examining the effectiveness of a strategy to improve adherence to tuberculosis treatment in a resource-poor setting, the intervention package based on improved patient counseling and communication, decentralisation of treatment delivery, patient choice of DOT supporter, and reinforcement of supervision activities led to improved patient outcome compared with the usual tuberculosis control procedures [40]. In addition to good communication skills in healthcare workers, attention to the management of the treatment associated side-effects and risk of nonadherence, and maintaining respect for patient autonomy and integrity are of paramount importance [41]. One study has further demonstrated that both family-member and community DOTS strategies can attain international targets for treatment success under programme conditions [42].

Fixed-dose combination formulations

The use of fixed-dose combination (FDC) formulations comprising two, three or even four drugs may enhance ease of prescription for physicians, reduce inadvertent medication errors, simplify drug procurement and supply, improve treatment adherence by patients, and, thereby, decrease the risk of development of MDR tuberculosis [43, 44]. In a study that compared the levels of acquired drug resistance in patients who had rifampicin and isoniazid FDC, under self-administration settings, the rate was as low as 0.2%, given the limitations of the investigation [45]. WHO has included some FDC tablets in its list of essential drugs [46]. Only formulations of proven good quality should be used [47]. The majority of studies found no significant difference between FDC tablets and single drugs regarding sputum smear conversion rates, side-effects and relapses [48, 49]. However, a Singapore study found higher relapse rates at 2 and 5 yrs of follow-up in patients who received FDC tablets [50]. Furthermore, FDC tablets cannot replace treatment supervision completely, as there is still a potential risk of the emergence of drug resistance when these combination tablets are taken irregularly [51].

Future possibilities for rifamycin use

Studies have demonstrated the bactericidal and sterilising activities of rifampicin, as well as their dose and concentration dependence [52–54]. In one study, the maximum dosage of rifampicin tested was 20 $mg \cdot kg^{-1}$ [53]. Rifampicin at a dosage of >10 $mg \cdot kg^{-1}$ may also suppress or delay emergence of resistance [54]. Early chemotherapy trials that evaluated the use of high-dose rifampicin have shown better 1- or 2-month bacteriological conversion but not a more favourable relapse rate, probably due to absence of the inclusion of pyrazinamide in the treatment regimens [55]. The safety and tolerability of high-dose rifampicin were not meticulously assessed in the early chemotherapy trials, leaving potential concern over these issues.

Although rifampicin hepatotoxicity was thought to be idiosyncratic in nature [56], it is not possible to exclude interactive toxicity between isoniazid and rifampicin [57]. Thus, it may not be entirely appropriate to extrapolate safety data from the use of high-dose rifampicin in treatment of other bacterial infections, such as brucellosis [55]. In fact, mild hepatotoxicity occurred more frequently in a study among patients who received high-dose rifampicin for tuberculosis treatment, although no patient developed serious hepatotoxicity [58]. ''Flu-like'' syndrome has also been associated with high-dose rifampicin, but mainly for intermittent rifampicin administration, and it generally occurs after 3 months of drug administration [59]. Thrombocytopenia, haemolytic anaemia and acute renal failure may also occur. Since these reactions are immunological in origin, they are not likely to occur more frequently when a higher dosage of rifampicin is used [59]. Further clinical trials would be needed to examine whether such a strategy could enhance bacillary sterilisation and shorten tuberculosis therapy without excessive adverse effects [60]. A phase II clinical trial is being conducted to compare the pharmacokinetics and pharmacodynamics of daily doses of 900 and 1,200 mg rifampicin with the standard 600-mg dose during the 2-month intensive phase of treatment [61].

Early trials of rifapentine, a long-acting cyclopentyl rifamycin with a plasma half-life of 14 h, given in a 600-mg dose together with isoniazid on a once-weekly basis during the continuation phase of treatment in patients with tuberculosis have shown satisfactory efficacy in a subgroup of HIV-negative patients with noncavitary disease and limited bacterial burden, despite an overall failure/relapse rate of 10% [62, 63], and emergence of rifamycin monoresistance in relapse cases among HIV-positive subjects [29]. It has been shown that a 900-mg dose of rifapentine had superior pharmacokinetics to the 600-mg dose [64, 65], and that a 1,200-mg dose of rifapentine produced an optimum pulse and post-antibiotic lag on the growth of *M. tuberculosis* [52]. In a murine model, twice-weekly regimens containing rifapentine (15–20 $mg \cdot kg^{-1}$) have shown marked antituberculosis potency by enhancing the rifamycin exposure [66] and preliminary data using daily dosing of rifapentine have also been encouraging [67]. Rifapentine autoinduction of metabolism has also been noted with interest [68]. Currently, there are only sufficient data on the safety and good tolerance of rifapentine dosed at 900 mg once-weekly [69]. However, in

an ongoing phase II clinical trial, rifapentine dosed at 10 mg·kg^{-1} 5 days·week^{-1} is being administered [70], and no unusual preponderance of adverse events was reported by the Data and Safety Monitoring Committee so far.

CHEMOTHERAPY OF PULMONARY MDR AND XDR TUBERCULOSIS

The clinical relevance of antituberculosis drug resistance will be reviewed first as a background to the treatment of drug-resistant tuberculosis, especially the MDR and XDR forms.

Clinical relevance of antituberculosis drug resistance

Resistance to an antituberculosis drugs arises spontaneously through chromosomal mutation at a frequency of 10^{-6}–10^{-8} bacterial replications [36]. The chromosomal loci involved are distinct for the major classes of drugs. Thus, when three or more effective drugs are used in combination, spontaneous emergence of mutants resistant to all drugs is most unlikely with the usual bacterial load in the diseased host. However, sequential genetic mutations may be amplified through human error, resulting in clinically drug-resistant tuberculosis. These include ''monotherapy'' due to irregular drug supply, inappropriate doctor prescription and poor patient adherence to treatment [36]. Subsequent transmission of resistant *M. tuberculosis* strains from the index patient to others, as facilitated by diagnostic delay and infection-control breach, aggravates the problem [71]. A recent review regarding epidemiology of MDR tuberculosis showed that the risk factors for drug resistance pertain to those facilitating the selection of resistance in the community and the specific conditions that appear to increase the vulnerability of some patients, such as in certain HIV or malabsorption settings. The epidemiological situation is principally related to poor treatment practices and poor implementation of control programmes [71].

Isoniazid resistance is the most common form of drug resistance encountered, whether in isolation or in combination with other drugs [2]. Standard short-course chemotherapy for isoniazid-resistant tuberculosis can achieve good success (>95% cure rate) when all four drugs are used throughout the 6 months of treatment (grade B) [21]. When the four drugs are reduced to only rifampicin and isoniazid after 2 months, the relapse rate after 6 months of treatment rises to 10% [22]. As there may be a genuine chance of resistance amplification with additional resistance to rifampicin [20, 72] (especially for HIV status and/or intermittent dosing [20, 28, 31]) some authorities recommend changing to alternative regimens, such as REZ or RE, for more prolonged durations of administration, often ⩽1 yr (grade D) [73, 74]. Currently, the most optimal regimen for treatment of isoniazid-resistant tuberculosis appears unknown [16].

Rifampicin-resistant tuberculosis carries a much more ominous prognosis, as the outcome of standard short-course regimens for such disease is poor, in terms of both disease status on cessation of treatment and subsequent relapse [75]. A recommendation has been made to treat such disease with EHZ for 18–24 months (grade D) [76]. Some authorities feel that the duration of treatment can be shortened to 12 months by the addition of a fluoroquinolone to this three-drug regimen (grade D) [24]. Furthermore, rifampicin monoresistance in *M. tuberculosis* is usually rare, except perhaps in HIV-infected patients [28, 31, 76, 77]. Thus, rifampicin resistance generally serves as a surrogate marker for dual resistance to rifampicin and isoniazid, *i.e.* MDR tuberculosis [78, 79], especially for previously treated patients. Short-course chemotherapy can cure <60% of MDR tuberculosis cases [80], with a high recurrence rate of ~28% among those with apparent success [81]. A recent analysis has shown that the currently recommended short-course treatment regimens for both initial and retreatment purposes could not achieve good outcomes (for failures, relapses and deaths) in countries having initial MDR rates >3% [82]. It is quite clear today that alternative specific chemotherapy using second-line drugs is required for the management of this formidable condition [83].

Increased risk for development of bacillary resistance to ethambutol and pyrazinamide likely occurs when a conventional four-drug regimen for initial treatment and a conventional five-drug retreatment regimen are repeatedly administered despite observed treatment failure with the conventional short-course regimens for tuberculosis [84–86]. Pyrazinamide and/or ethambutol resistance, in addition to dual resistance to isoniazid and rifampicin, generally portends a more adverse prognosis in MDR tuberculosis [87], particularly when patients receive only standardised second-line antituberculosis drug regimens with pyrazinamide and ethambutol plus a fluoroquinolone and aminoglycoside or capreomycin.

Fluoroquinolones are generally regarded as having a pivotal role in the treatment of MDR tuberculosis [88–90]. *In vitro* resistance to fluoroquinolones has been shown to predict a poor outcome in the treatment of MDR tuberculosis [88, 91, 92]. Most fluoroquinolone resistance in *M. tuberculosis* is associated with the injudicious use of this class of drugs in the management of tuberculosis, particularly MDR tuberculosis [93, 94], including the use of suboptimal second-line drug regimens comprising an inadequate number, dosage and/or quality of accompanying agents [84]. Overzealous use of this class of antimicrobials in the treatment of lower respiratory tract and other community-acquired infections might also contribute to development of fluoroquinolone-resistant tuberculosis [95].

As the aminoglycosides and capreomycin have potent antituberculosis activity, the loss of these second-line injectables, together with fluoroquinolones, through their suboptimal use in the management of MDR tuberculosis would result in XDR tuberculosis, which, in general, carries a worse prognosis [96].

Programme strategies and implementation

The emergence of drug resistance in *M. tuberculosis* has prompted WHO to modify the DOTS strategy to a more comprehensive approach, the Stop TB strategy [97]. This strategy comprises the following components: 1) pursuit of high-quality DOTS expansion and enhancement; 2) addressing tuberculosis in HIV patients, MDR tubercuosis and the needs of poor and vulnerable populations; 3) contribution to health system strengthening based on primary healthcare; 4) engaging all care providers; 5) empowering people with tuberculosis care, and communities through partnership; and 6) enabling and promoting research. The management of MDR tuberculosis through the use of alternative second-line antituberculosis chemotherapy mandates its delivery on a programmatic basis,

with five key components built on the DOTS framework (fig. 1). The capacity for performing drug susceptibility testing and availability of second-line drugs are not adequate to achieve cure. Other factors, such as a set of standard procedures, clear guidelines on treatment and follow-up of patients and administration of DOT, must be included in the programme for MDR tuberculosis management to attain good results [83]. There are basically three possible programmatic approaches for the management of MDR tuberculosis [83]: 1) standardised treatment, in which regimens are designed on the basis of representative drug-resistance surveillance data of specific treatment categories, with all patients in the same group or category being treated by the same regimen; 2) empirical treatment, in which each patient's regimen is individually designed on the basis of the previous history of antituberculosis therapy with the help of representative drug-resistance surveillance data, followed by regimen adjustment when the individual drug susceptibility testing results are known; 3) individualised treatment, in which each patient's regimen is designed on the basis of previous history of antituberculosis treatment and individual drug susceptibility testing results.

While a standardised regimen enables simple operation and broadens access to care, there may be concern over the amplification of multidrug resistance if the number of available second-line drugs in the regimen is low [98, 99]. Individualised treatment strategies rely heavily on capable laboratory services, but have the advantage of avoiding placing patients on toxic and expensive drugs to which the *M. tuberculosis* strain is resistant. One caveat, however, is the unsatisfactory reliability of second-line drug susceptibility testing results for many agents aside from the fluoroquinolones and the injectables, arising partly from the difficulty in standardising testing methodology [100–102]. However, some progress has been made accordingly [103]. Patients who had previous treatment with second-line drugs would probably benefit more from the administration of individualised regimens. When re-treated patients are presumed to have a high likelihood of MDR tuberculosis, an empirical regimen can be administered while awaiting the results of conventional drug susceptibility testing [16].

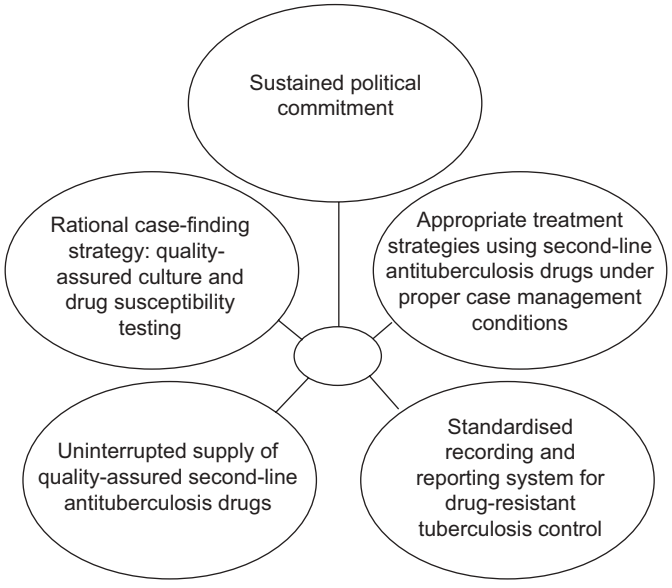

FIGURE 1. Directly observed treatment, short-course (DOTS) framework applied to the management of drug-resistant tuberculosis. Reproduced and modified from [83] with permission from the publisher.

Regardless of the strategy advocated, there are significant cost issues in the management of MDR tuberculosis patients [104]. In a previous decision analysis, it was shown that more patients would die from tuberculosis if the implementation of a drug resistance programme is associated with even minimal decreases in the effectiveness of DOTS [105]. Nevertheless, the feasibility and cost-effectiveness of treatment of MDR tuberculosis is now quite well established, even in resource-limited settings [106, 107]. In countries with significant financial difficulties, additional support, besides technical assistance, from international organisations and governments of industrialised countries would be needed, further to that obtained from local governments [108]. In this regard, the Green Light Committee of the Stop TB Partnership, involving WHO and collaborators, has played a significant role in helping the implementation of these programmes in countries with an affordability problem in the management of MDR tuberculosis [109].

Design of drug regimens

Guidelines on the treatment of MDR tuberculosis are often formulated based on experience and observational studies, as data from randomised trials are lacking. A detailed review has addressed the evidence and controversy of treatment of MDR tuberculosis, focusing on the number of antituberculosis drugs required to treat MDR tuberculosis, the most rational use of effective drugs against the disease, the advisable length of parenteral drug administration or of the initial phase of therapy, the contribution of surgery to the management of MDR tuberculosis, and the optimal approach for treating MDR disease (standardised *versus* individualised regimens). However, little evidence, but much controversy, was found regarding the the treatment of MDR tuberculosis [110]. Randomised controlled trials regarding chemotherapy of MDR tuberculosis should be undertaken to provide more evidence-based recommendations [111]. The updated WHO guidelines in 2008 and 2009 recommend designing treatment regimens with a consistent approach based on the hierarchy of five categories of antituberculosis drugs (table 3) [16, 112]. The potency of these drugs is in a descending order; thus, the drugs are selected from these five groups accordingly. A brief review of the utility of these drugs is detailed below.

While isoniazid in conventional doses has limited usefulness, high-dose isoniazid (>10 $mg \cdot kg^{-1}$) has demonstrated some efficacy (clinical, bacteriological and radiographic) as well as reasonable patient tolerance in a recent study [113]. After adjustment for potential confounders, subjects who received high-dose isoniazid had a 2.37-fold higher likelihood of becoming culture-negative at 6 months. Isoniazid-resistant *M. tuberculosis* organisms belonging to the low-resistance phenotype often have cross-resistance to ethionamide, while those of the high-resistance phenotype are more susceptible. Adding high-dose isoniazid kills the former, leaving the latter that are more susceptible to the ethionamide included in the MDR tuberculosis regimen. Ethambutol and pyrazinamide

TABLE 3 Categories of antituberculosis drugs

Category 1: first-line oral drugs
Isoniazid
Rifampicin
Ethambutol
Pyrazinamide
Category 2: fluoroquinolones
Levofloxacin
Moxifloxacin
Ofloxacin
Category 3: injectable agents
Capreomycin
Amikacin
Kanamycin
Streptomycin
Category 4: oral bacteriostatic second-line agents
Ethionamide
Prothionamide
Para-aminosalicylic acid
Cycloserine
Terizidone
Category 5: agents with efficacy that is not totally clear (not generally recommended by WHO for routine use in treating patients with drug-resistant tuberculosis)
Isoniazid (high-dose; >10 mg·kg^{-1})
Linezolid
Amoxicillin–clavulanate
Clarithromycin
Clofazimine
Meropenem plus clavulanate
Thiacetazone
Rifabutin

WHO: World Health Organization. Reprodued and modified from [16] with permission from the publisher.

should be included in the treatment regimen if they are likely to be effective from laboratory evidence or clinical history.

Fluoroquinolone (Category 2) therapy is independently associated with better treatment outcomes. Losing this drug category increases risk of death and failure [89, 114]. Thus, a fluoroquinolone should be included whenever possible, although potential cross-resistance among the class members may hamper their utility in XDR tuberculosis [115]. Older fluoroquinolones, especially ciprofloxacin, are not recommended, as there could be a slower sputum culture conversion and a higher relapse rate [116]. Newer fluoroquinolones, moxifloxacin and levofloxacin, can be active against some ofloxacin-resistant strains of *M. tuberculosis* [117, 118].

With the high rate of streptomycin resistance among MDR bacillary strains, an injectable agent from Category 3, amikacin, capreomycin or kanamycin, should form part of the regimen, as far as possible. Capreomycin may have a further advantage, owing to its incomplete cross-resistance with kanamycin and amikacin in some *M. tuberculosis* strains [119, 120]. However, variable cross-resistance exists among these three second-line injectables. Injectable agents are generally recommended for $\geqslant$6 months, or 4 months after culture conversion, with modification according to bacillary resistance or patient intolerance [83].

Category 4 agents are generally less efficacious and more difficult to tolerate. Cycloserine/terizidone have potentially serious neurotoxicity. The use of thioamides and *para*-aminosalicylic acid are notoriously associated with gastrointestinal reactions and other adverse events [83, 117]. They are added according to estimated bacillary susceptibility, drug history, efficacy, side-effect profile and cost.

Category 5 drugs, including linezolid, amoxicillin–clavulanate, meropenem/clavulanate and clofazimine, are not generally recommended in drug-resistant tuberculosis, because their roles are uncertain [112]. However, they have potential role in situations without other options, especially in patients with XDR tuberculosis [16, 121].

Clinical experience on linezolid has been slowly accumulating after the first report of its good *in vitro* activities against *M. tuberculosis* a decade ago [122]. In one study, nine out of 10 MDR tuberculosis patients given linezolid and other drugs in a DOT setting were cured, despite substantial haematological and neurological toxicities [123]. Use of linezolid at half dose (600 mg·day^{-1}) helped to reduce bone marrow suppression, but not peripheral and optic neuropathy [124]. Fatal lactic acidosis can also occur after prolonged therapy [125]. A sizeable retrospective study has confirmed these adverse effects [126]. Most of them occurred after 60 days of therapy [126]. More major side-effects occurred with twice-daily than once-daily dosing, with no difference in efficacy. Outcomes were similar in patients treated with or without linezolid, although linezolid use was assocated with more extensive resistance to first- and second-line drugs. Thus, it appears that linezolid (600 mg once-daily), when added to an individualised multidrug regimen, may improve bacteriological conversion and treatment success in the most complicated MDR or XDR tuberculosis cases [126]. Its use might not be warranted where better tolerated alternatives are available. Further evaluation of linezolid at a dose of 600 mg·day^{-1} is being conducted in a phase I/II clinical trial in South Africa [127]. Linezolid (300 mg·day^{-1}), in addition to good tolerance, appeared to have reasonable efficacy in a recent study [128]. However, concerns have been raised regarding the method of analysis and possible emergence of drug resistance [129]. Another oxazolidinone, PNU-100480, has demonstrated more potent activity *in vitro* and in a murine model [130], while AZD5847 is undergoing phase I trial in healthy volunteers [131].

Amoxicillin–clavulanate has some early bactericidal effect against *M. tuberculosis* [132] and distinct inhibitory activity on MDR strains [133]. Other β-lactam–β-lactamase inhibitor combinations have also shown similar *in vitro* activity [134], but clinical efficacy data are limited [135, 136]. Imipenem/cilastatin is active against MDR and XDR strains *M. tuberculosis in vitro* [137]. There are also some limited efficacy data of imipenem in mice and humans [138]. When meropenem, a carbapenem (a newer congener of imipenem), was combined with the β-lactamase inhibitor clavulanate, potent activity against laboratory strains of *M. tuberculosis* was observed, with sterilisation of aerobically grown cultures achieved within

14 days [139]. In addition, this combination exhibited activity against anaerobically grown cultures that mimic the mycobacterial persisters, and inhibited the growth of 13 XDR strains of *M. tuberculosis* at the same levels as observed for drug-susceptible strains [139]. Thus, meropenem–clavulanate might have a potential role in the treatment of tuberculosis [140].

Clofazimine, a riminophenazine, and some of its analogues, have been shown to possess *in vitro* and *in vivo* activities against *M. tuberculosis*, including drug-resistant strains [141, 142]. Clofazimine is primarily used in the treatment of leprosy but is sometimes incorporated in the treatment regimens for MDR tuberculosis, although data on its clinical efficacy [143] and tolerance [144] are limited and conflicting. Rifabutin has very limited potential utility in treatment of MDR tuberculosis due to its high cross-resistance rate with rifampicin [16].

MDR and XDR tuberculosis should be treated aggressively. The fluoroquinolones and injectables are the most potent second-line agents for MDR tuberculosis (grade C). In the initial 6 months, the treatment regimen should consist of at least four noncross-reacting drugs to which the organism is, or is likely to be, susceptible (grade C). Generally speaking, those patients who have previously received second-line drugs are more likely to need a higher number of drugs, as do patients with more extensive radiographic disease and more formidable drug resistance patterns. The use of capreomycin/kanamycin/amikacin, fluoroquinolone, ethambutol, pyrazinamide and ethionamide/prothionamide for disease with bacillary resistance to RH (with or without S), and the use of capreomycin/kanamycin/amikacin, fluoroquinolone, ethionamide/prothionamide, cycloserine and *para*-aminosalicylic acid for disease with bacillary resistance to RHEZ (with or without S) constitute important examples of these regimens. The possibility of further acquired resistance should be considered. A single drug should never be added to a failing regimen, for fear of selecting mutants that are resistant to the newly added drug (addition phenomenon) [84]. Care is also warranted in chemotherapy trials involving newly developed antituberculosis drugs. Linezolid resistance among *M. tuberculosis* is fairly well known today, and may serve as a warning [145, 146].

The dosages of second-line drugs used in the treatment of MDR and XDR tuberculosis are listed in table 4 [83, 112, 147]. The maximum dosage of cycloserine and ethionamide/prothionamide should generally be 750 mg when once-daily dosing is used, as there is concern over toxicity for higher doses. The same likely applies also for aminoglycosides/capreomycin given three to five times per week [147]. Some of the patients weighing >70 kg might tolerate 1,000 mg for these three classes of drugs [112]. The maximum once-daily dosage of moxifloxacin and levofloxacin is 400 mg and 750–800 mg, respectively. While the efficacy of 1,000 mg levofloxacin per day is high [148], the tolerance data are still limited.

WHO recommends a treatment duration of $\geqslant$18 months after culture conversion, even for HIV-negative patients (grade D) [83]. However, a proportion of immunocompetent patients who managed to achieve sustained sputum culture conversion early might be adequately treated with 12 months of fluoroquinolone-containing regimens [88, 149]. It appears, however, that patients who are immunocompromised (including those with diabetes mellitus and silicosis), or have extensive radiographic evidence of disease (particularly with cavities), extensive drug resistance, delayed sputum culture conversion (*i.e.* after >3 months of chemotherapy) or extrapulmonary involvement should receive >12 months of therapy [88].

Another important principle in the chemotherapy of MDR and XDR tuberculosis is to exercise vigilance to prevent and manage adverse reactions.

Second-line drugs for treating MDR tuberculosis are generally more toxic and difficult to tolerate. In a study on MDR tuberculosis in Hong Kong, ~40% of the patients experienced adverse drug reactions of varying severity [88]. However, only half of the patients required modification of their drug regimens. These results corroborated the findings of a study of MDR tuberculosis patients in Peru, where the adverse drug reactions never resulted in discontinuation of antituberculosis therapy and only occasionally (11.7%) resulted in suspension of an agent [150]. In a reported series of MDR tuberculosis patients in Turkey, ~70% of the patients experienced adverse effects to the second-line agents and 55.5% required treatment modification [151]. With timely and appropriate management, the treatment success rate (77.6%) did not appear to be markedly compromised. Indeed, the results from Turkey largely paralleled those pooled from five sites (Estonia, Latvia, Peru, The Philippines and Russia) in resource-limited settings [107].

The second-line antituberculosis drugs are handled in patients by different pathways, including diverse metabolic ones. There is a potential for their interaction with different classes of antiretroviral drugs [152].

Close clinical monitoring is necessary to ensure that adverse drug effects are recognised quickly. Apart from clinical monitoring, ancillary investigations, such as audiometry screening, vestibular assessment and biochemical tests, including those of liver and renal functions, electrolytes, and thyroid functions, are helpful. In addition to assessment of visual acuity, tests to detect peripheral neuropathy are occasionally needed. The optimal intervals at which these investigations should be performed are unknown. Physicians should be aware that some of the adverse effects that can occur during the continuation phase of an extended course of antituberculosis therapy can emerge within a few days. When an adverse reaction is mild and not dangerous, such as a gastrointestinal one, continuation of therapy alongside supportive treatment is sufficient. If an adverse event is severe or potentially dangerous, such as a neurological effect, a more intensive management strategy embracing supportive treatment and drug discontinuation or dosage adjustment is required [83]. Psychosocial support is also an important element in the management of adverse reactions. Education, counselling and encouragement can all contribute to a successful outcome [83].

Patients developing nephrotoxicity were found to have a significantly longer duration of treatment with aminoglycosides and received a higher total dose. Predisposing factors for ototoxicity of aminoglycosides are less well characterised, except perhaps for old age, renal impairment and prolonged therapy [153]. Ototoxicity due to aminoglycosides can be

TABLE 4 Dosages of antituberculosis drugs used in treatment of multidrug-resistant tuberculosis in adults

Drug	Daily dosage[#] mg·kg^{-1}	Usual daily dosage[#] mg
Aminoglycosides and allied injectable peptide antibiotics		
Streptomycin	15	750[¶]
Kanamycin	15	750[¶]
Amikacin	15	750[¶]
Capreomycin	15	750[¶]
Fluoroquinolones		
Ofloxacin		600–800[¶]
Levofloxacin		500–750[¶,+]
Moxifloxacin[§]		400[¶]
Thioamides		
Ethionamide[f]	15	500–750[¶]
Prothionamide[f]	15	500–750[¶]
Oral bacteriostatic first-line drugs		
Ethambutol	15	
Pyrazinamide	20–30	1000–2000[¶]
Oral bacteriostatic second-line drugs		
Cycloserine[f]	15	500–750[¶]
Terizidone[f]	15	600[¶]
Para-aminosalicylic acid[##]	200	8000–12000[¶]
Thiacetazone[¶¶]	2.5	150[¶]
Oral reserve drugs with uncertain/not totally clear antituberculosis activities		
Clofazimine[§]		100[¶]
Amoxicillin–clavulanate[§,##,++]		875–125[¶] *b.i.d.* or 500–250[¶] *t.i.d.*
Linezolid[§,##,++]		600[¶] *b.i.d.* or 600

[#]: drugs are generally given on a daily basis except for aminoglycosides and the allied injectable antibiotics, which are given three to five times per week, as well as those otherwise specified; [¶]: usually the maximum daily dosage (some of the patients weighing >70 kg can tolerate higher dosages; see main text); [+]: higher dosage usually given for fluoroquinolone-resistant disease; [§]: optimal dosage not fully delineated; [f]: may require administration in two split doses per day; [##]: requires administration in split doses per day; [¶¶]: should only be used in patients documented to be HIV-negative, and usually not be chosen over other oral bacteriostatic second-line drugs; [++]: long-term safety not fully confirmed.

irreversible and patients need to be counselled to report symptoms at the earliest signs of occurrence.

Treatment outcomes

Treatment outcomes of MDR and XDR tuberculosis vary greatly between studies [88–90, 92, 154–167], possibly related to variations in method of analysis, definition of treatment success and failure, drug susceptibility testing, clinical follow-up, and missing data. The outcomes also likely depend on adverse events due to drugs and their management, as well as supply and availability of the agents for treatment.

For MDR tuberculosis, success rates (cures and treatment completions) are around 50–70% [88–90, 92, 154–167]. In a recent systematic review [168], the MDR tuberculosis treatment success rate improved with treatment duration of ⩾18 months and DOT throughout treatment. Studies that combined both factors had significantly higher pooled success rate than other studies (69 *versus* 58%). Individualised treatment regimens conferred a higher success rate (64%) than standardised regimens (54%), although the difference was not statistically significant. In general, patients with XDR tuberculosis had worse treatment success rates (⩽50%) [164–166], although one study has shown a remarkable treatment success rate of 60.4%, which is comparable with that (66.3%) of MDR tuberculosis in the same locality [169].

Prior antituberculosis therapy [89, 90, 92, 154, 157, 167], extensive *in vitro* drug resistance [87, 89, 92, 157, 165], fluoroquinolone resistance [88, 90, 92, 158, 167] or prior fluoroquinolone use [158], capreomycin resistance [96], positive sputum smear [167], radiological cavitation [88, 89, 158], HIV seropositivity [156, 161, 163, 166, 167], other immunocompromised states [159], history of incarceration [92], low body mass index (<18.5 or <20 kg·m^{-2}) [92, 160], hypoalbuminaemia [164], older age [89, 158], male sex [154], low haematocrit [160], and early (<1 yr of treatment) default [163] constitute important risk factors for poor outcomes.

In a recent systematic review of XDR tuberculosis, it was shown that strategies to support adherence, as well as psychological, nutritional and even financial interventions, might further contribute to improved outcomes in patients with XDR tuberculosis [170]. Encouraging results from some countries in Asia and Europe have also suggested that management in specialised reference centres could improve outcome, although high success rates could be achieved with treatment in some community settings [170].

The impact of HIV on the outcomes of MDR and XDR tuberculosis has been most serious in South Africa. Among 272 MDR and 382 XDR tuberculosis patients with HIV coinfection rates of 90% and 98%, 1-yr mortality was 71% and 83%, respectively. This mortality improved, however, from 2005 to 2007, though the majority of death still occurred within the first 30 days [166]. In the systematic review mentioned earlier [170], it was remarked that additional data for HIV-infected individuals would be required to determine the role of HIV coinfection in XDR tuberculosis treatment outcome, and to evaluate interventions that might contribute to improve outcomes in HIV-infected XDR tuberculosis. The high case-fatality rate in the Tugela Ferry outbreak could represent a combination of factors at play, not only host immunocompromisation, but also lack of access to adequate diagnosis and treatment [170].

Palliative management and end-of-life care

At a certain point in time, recourse to palliative care is indicated for selected patients with ''difficult'' MDR or XDR tuberculosis, in the interest of both the individual patient and the community as a whole. Such management aims to provide uninterrupted medical and psychological care, as well as to ensure a dignified end of life for the patient [83, 147].

NEW DRUGS FOR TREATMENT OF TUBERCULOSIS

New antituberculosis drugs are needed to simplify treatment of drug-susceptible tuberculosis and to improve outcome of drug-resistant tuberculosis [171]. Only four compounds will be discussed in detail for the purpose of this article, as these drugs appear to have sufficient potential for use in improving tuberculosis therapy in the coming decade.

Moxifloxacin

Moxifloxacin is an 8-methoxyfluoroquinolone with a long plasma half-life of ~11 h. It has potent bactericidal and sterilising activity against *M. tuberculosis*, as shown in murine studies [172, 173]. In the TB Trials Consortium (TBTC) Study 27, a phase II trial, substituting moxifloxacin for ethambutol in the first 8 weeks of therapy did not change the 2-month culture negativity rates (71%), but there appeared to be higher activity at earlier time point [174]. However, a study with nearly the same design conducted in Brazil has shown better culture conversion (80%) in patients receiving moxifloxacin during the initial phase of treatment compared with the ethambutol arm (63%) [175]. Another similar phase II clinical study has also shown that patients in the moxifloxacin arm cleared their sputum bacilli more quickly [176]. Based on the rapid sterilisation results of the isoniazid-sparing regimen in murine models, TBTC Study 28 was designed as a double-blind, placebo-controlled study to evaluate 2-month culture conversion rates with the substitution of moxifloxacin for isoniazid in the 2-month intensive phase of treatment of pulmonary tuberculosis. Only a small nonsignificant increase in the 2-month culture negativity was achieved [177]. More rapid sputum culture conversion was also observed with the addition of moxifloxacin to the standard short-course regimen in a nonrandomised study [178]. In these studies, moxifloxacin appeared to be well tolerated by most patients, apart from an increased incidence of nausea. QTc interval prolongation was observed in some patients, but this might not have clinical significance [175, 177]. Further evaluation of the fluoroquinolone is ongoing in a phase III REMox study [179]. This study will explore whether moxifloxacin substitution for isoniazid or ethambutol can shorten the conventional therapy from 6 to 4 months.

Moxifloxacin- and rifapentine-based regimens are also under investigation. It should be noted that, when these drugs are given together, rifapentine may induce enzymes that metabolise moxifloxacin, resulting in modestly reduced moxifloxacin concentrations [68]. Using a murine model of tuberculosis, regimens consisting of isoniazid or moxifloxacin plus rifapentine and pyrazinamide, administered either daily or three-times-weekly, were evaluated for bactericidal activity and treatment-shortening potential. The duration of treatment necessary to achieve stable cure was 10 weeks for daily regimens and 12 weeks for three-times-weekly regimens, regardless of whether isoniazid or moxifloxacin was used with rifapentine and pyrazinamide [180]. By contrast, under the 12-week regimen of RHZ, all mice relapsed. The treatment-shortening potential of more frequent and/or higher doses of rifapentine than 600 mg once-weekly are being explored in both animal experiments and clinical trials, as discussed in the section on treatment of smear-positive pulmonary tuberculosis. Furthermore, in a phase II clinical trial that commenced in 2009, smear-positive pulmonary tuberculosis patients were randomised in the initial 2 months to receive either H-rifapentine-Z-moxifloxacin or RHEZ, followed by the standard nonexperimental regimen in the continuation phase. The efficacy in terms of sputum conversion rates and treatment outcomes, as well as safety and tolerability of the rifapentine–moxifloxacin-containing regimens, will thus be evaluated [181]. Notwithstanding these somewhat encouraging results, the high rates of fluoroquinolone-resistant tuberculosis in many parts of the world, especially when coinciding with high disease burden, pose concern regarding the potential utility of the new fluoroquinolones in shortening tuberculosis treatment [182]. Regarding the role of moxifloxacin in the treatment of MDR and XDR tuberculosis, there have been some promising results lately [183], although the issue of partial cross-resistance among *M. tuberculosis* strains is still cause for concern [184].

TMC207

TMC207 is a novel diarylquinoline with unique activity on the mycobacterial adenosine triphosphate (ATP) synthase [185]. It is active against both drug-resistant and -susceptible *M. tuberculosis*, as well as other mycobacterial species. It has a long half-life in plasma and tissues of nearly 24 h. Data have also suggested that TMC207 might kill dormant bacilli as effectively as aerobically grown bacilli. TMC207 is metabolised by cytochrome P450 3A4; thus, its plasma level may be reduced by half through interaction with rifampicin. However, data from a mouse model have demonstrated that TMC207 had significant activity, even when its exposure was reduced by 50% and it was added to a strong background regimen of RHZ. The bactericidal effect of TMC207 in mice was modest during the first week of treatment but increased in the following three weeks [186]. TMC207 probably acts synergistically with pyrazinamide to exert sterilisation activity. In the mouse model, 2-month treatment regimens containing TMC207 and pyrazinamide led to sterilisation, suggesting

treatment-shortening potential [187]. In another mouse model study, the triple combination of TMC207–rifapentine–pyrazinamide, given once weekly, was more active than the current regimen of RHZ given five times per week and led to satisfactory lung culture negativity at 2 months [188]. Such unprecedented activity has suggested that it might be feasible to develop a fully intermittent, once-weekly regimen.

In a mouse model to evaluate the use of TMC207 in MDR tuberculosis, treatment was given five times per week with TMC207 alone or various combinations of TMC207 plus pyrazinamide or other second-line drugs [189]. All TMC207-containing regimens were significantly more active than the non-TMC207-containing regimens after 1 month of therapy.

An early bactericidal activity study with ascending doses of TMC207 has demonstrated a delayed onset of bacteriolysis, with significant activity from day 4–7 when given at a daily dose of 400 mg, which was similar in magnitude to those of isoniazid and rifampicin over the same period [190].

A double-blind, randomised phase II clinical trial with TMC207 in MDR tuberculosis patients began in 2007 [191]. The study is being conducted in two consecutive stages. In the first exploratory stage for safety and dose determination, newly diagnosed sputum smear-positive patients with MDR tuberculosis were randomised to receive either TMC207 or placebo for 8 weeks on top of a background regimen. The dosing scheme for TMC207 was validated for further testing in the second stage, being 400 mg daily for 2 weeks followed by 200 mg three times weekly. In the second stage planned for proof of effectiveness, patients are randomised to receive either TMC207 or placebo for 24 weeks on top of a background regimen. After finishing 24 weeks of treatment, patients will continue to receive MDR tuberculosis treatment as per national treatment guidelines. Study subjects will be followed for safety, tolerability, pharmacokinetics and microbiological efficacy for 96 weeks after receiving their last dose of TMC207 [191]. Preliminary results from the first stage indicated high efficacy (faster rate and higher proportion of culture conversion) and good tolerance of TMC207 [192]. Further results are awaited with great interest. Like moxifloxacin, QTc prolongation with uncertain clinical significance was observed in some patients, aside from gastrointestinal upset [192]. TMC207 can have a role in treatment of MDR and XDR tuberculosis, subjected to confirmation of its tolerance and safety on long-term use. Its interaction with rifampicin might hamper its utility in treatment of drug-susceptible tuberculosis.

OPC-67683

OPC-67683 is a nitroimidazole with high potency *in vitro* and *in vivo* against *M. tuberculosis*, inclusive of MDR strains. It probably acts through inhibition of cell wall biosynthesis, a mechanism similar to that of PA-824 [193], but is ~20 times more potent. OPC-67683 and PA-824 are closely related compounds and appear to show cross-resistance. OPC-67683 has a long half-life at ~7–8 h, with no cross-resistance or antagonistic activity with first-line antituberculosis drugs. In addition, it has promising intracellular post-antibiotic effects against *M. tuberculosis*, comparable to those of rifampicin [193]. In mice, 2 months of OPC-67683–rifampicin–pyrazinamide followed by a further 2 months of OPC-67683–rifampicin led to complete culture negativity, suggesting that OPC-67683 in combination with other existing drugs could potentially shorten tuberculosis therapy [193]. A randomised, double-blind, multicentre phase II clinical trial has been underway since 2008 to evaluate its safety, efficacy and pharmacokinetics in the treatment of MDR tuberculosis. In the first 56 days, patients receiving an optimised background regimen were randomised to receive either placebo or OPC-67683 at a dose of 100 or 200 mg twice-daily. Thereafter, the study subjects will complete their optimised background regimen [194].

PA-824

PA-824 is a nitroimidazopyran, a class of novel antibacterial agents. It is active against drug-susceptible and -resistant, and both dividing and nonreplicating *M. tuberculosis* [195]. From studying colony-forming unit counts in the lungs of mice, PA-824 showed bactericidal activity comparable to that of isoniazid in the first 8 weeks and sterilising activity comparable to that of HR in the continuation phase [196]. A follow-up experiment in mice showed advantages in relapse rate with the same combination of drugs when PA-824 was given at a higher dose of 100 $mg \cdot kg^{-1}$ [197]. With the novel combination of PA-824–moxifloxacin–pyrazinamide, mice were cured more rapidly than with the first-line regimen of RHZ, suggesting that this combination might radically shorten the treatment of MDR tuberculosis in humans [198].

No serious adverse events were reported in phase I single- and multiple-dose trials in healthy volunteers [199]. An extended early bactericidal activity study was conducted recently in South Africa, evaluating the efficacy, safety and pharmacokinetics in newly diagnosed sputum smear-positive patients with drug-susceptible tuberculosis [200]. Based on findings from the pre-clinical and phase I studies, escalating doses of PA-824 were administered for 14 consecutive days to four groups of patients and compared with a fifth cohort receiving standard first-line antituberculosis treatment. The study showed substantial and continued early bactericidal activity over 14 days with equivalent efficacy at all doses from a daily dose of 200–1,200 mg. One important feature of PA-824 is its high protein binding (94%). Thus, it is necessary to ensure that sufficiently high concentrations of the free drug can be reached in cavities of pulmonary tuberculosis to exert bactericidal activity [201]. Both OPC-67683 and PA-824 appear to have potential roles in treatment of drug-susceptible and -resistant tuberculosis. Again, the most critical determinant would be their safety profiles.

Other potential candidates

Two important examples of other potential candidates include a pyrrole derivative, LL3858, and a diamine compound, SQ109. Both have been subjected to phase I testing and further progress is ongoing [55, 202, 203]. Other potential candidates would be those have both potent bactericidal and sterilising activities. Examples might include ATP synthase inhibitors, gyrase inhibitors and peptide deformylase inhibitors [203]. Aside from these new drugs under development, a neuroleptic thioridazine with impressive antituberculosis activity might also warrant repurposing to constitute a new agent for treating MDR and XDR tuberculosis [204].

ADJUNCTIVE SURGERY FOR PULMONARY TUBERCULOSIS

While chemotherapy using antituberculosis drugs constitutes the primary treatment modality for pulmonary tuberculosis, emergence of MDR and XDR tuberculosis has rekindled the enthusiasm in recourse to adjunctive surgery to improve the chance of cure in some patients in these drug-resistant scenarios [205]. Other indications of surgical treatment of tuberculosis centre on management of empyema, post-tuberculous bronchiectasis and mycetoma [206].

There are three basic selection criteria for adjunctive surgery in MDR tuberculosis patients [205]. These include: 1) drug resistance, as revealed by *in vitro* susceptibility testing, is so severe or extensive that there is a high probability of failure or relapse with medical therapy alone; 2) the disease is sufficiently localised that the great preponderance of radiographically discernible disease can be resected with an expectation of adequate cardiopulmonary capacity after surgery; and 3) drug activity is sufficient to diminish the mycobacterial burden to facilitate healing of bronchial stump after lung resection

Patients should receive chemotherapy prior to surgery for $\geqslant$3 months [205, 207]. If possible, they should be rendered culture-negative before lung resection. However, this may not always occur. In some cases, sputum culture conversion only appears with prolonged medical therapy after surgery. Ventilation/perfusion scan, pulmonary function tests and computed tomography of the chest are important investigations for pre-operative assessment [205, 206]. For some patients, assessment of pulmonary arterial pressure and bronchial tree anatomy/pathology need to be performed. Bilateral disease does not necessarily preclude surgical intervention, unless extensive [208]. Such disease would, however, require staged bilateral resection. In experienced hands, the outcome of lung resection has been found to be rather rewarding. The cure rates could reach $\geqslant$90% with post-surgery chemotherapy (table 5) [209–222]. In resource-limited areas, the cure rates might be lower (63–75%), but lung resection still appears useful as adjunctive management for this formidable disease [218]. However, adjunctive surgery necessitates expertise and financial instillation, which are often not readily available in many areas where MDR tuberculosis prevail [223].

Two rather sizable cohort studies have shown that the best outcomes in MDR tuberculosis patients were achieved by the use of fluoroquinolones and adjunctive surgery [89, 224]. Although there has been no randomised study to compare chemotherapy alone *versus* combined chemotherapy and surgery in the management of MDR tuberculosis, one recent small series reported significant and durable improvement with lung resection and post-operative first-line antituberculosis chemotherapy in patients with MDR and XDR tuberculosis [225]. This finding suggests the possibility of an independent role of lung resection in the management of these difficult drug-resistant scenarios.

With the emergence of XDR tuberculosis, adjunctive surgery becomes more relevant [121, 226]. Notwithstanding its use in some patients, the outcome of XDR tuberculosis is generally worse than that of MDR tuberculosis, with an overall success rate of ~50% [121, 227]. However, in selected patients, sustained sputum bacteriological conversion can be satisfactorily maintained [228]. From two large series, patients who had adjuvant surgery experienced better outcomes [89, 229].

Regarding the factors governing outcome of surgery for drug-resistant tuberculosis, a low body mass index ($<$18.5 kg·m^{-2}), bacillary resistance to fluoroquinolones and presence of cavity beyond the range of surgical resection portended poor prognosis in a carefully performed study [219]. The major complications of surgical treatment of pleuropulmonary tuberculosis include bronchopleural fistula, residual space

TABLE 5 Surgical treatment of multidrug-resistant tuberculosis[#]

First author [ref.]	Patients n	Treatment success %	Operative mortality %	Post-operative complications %
Treasure [209]	19	89	0	9
van Leuven [210]	62	75	2	23
Sung [211]	27	96	0	26
Pomerantz [212]	172	98	3	12
Chiang [213]	27	92	4	11
Park [214]	49	94	0	16
Naidoo [215]	23	96	0	17
Takeda [216]	26	89	3	14
Kir [217]	79	95	3	5
Somocurcio [218]	121	63	5	23
Kim [219]	79	72	1	23
Mohsen [220]	23	96	4	35
Wang [221]	56	87	0	25
Shiraishi [222]	56	98	0	16

[#]: most patients had lung resections in the form of pneumonectomy or lobectomy (a minority also had segmentectomy).

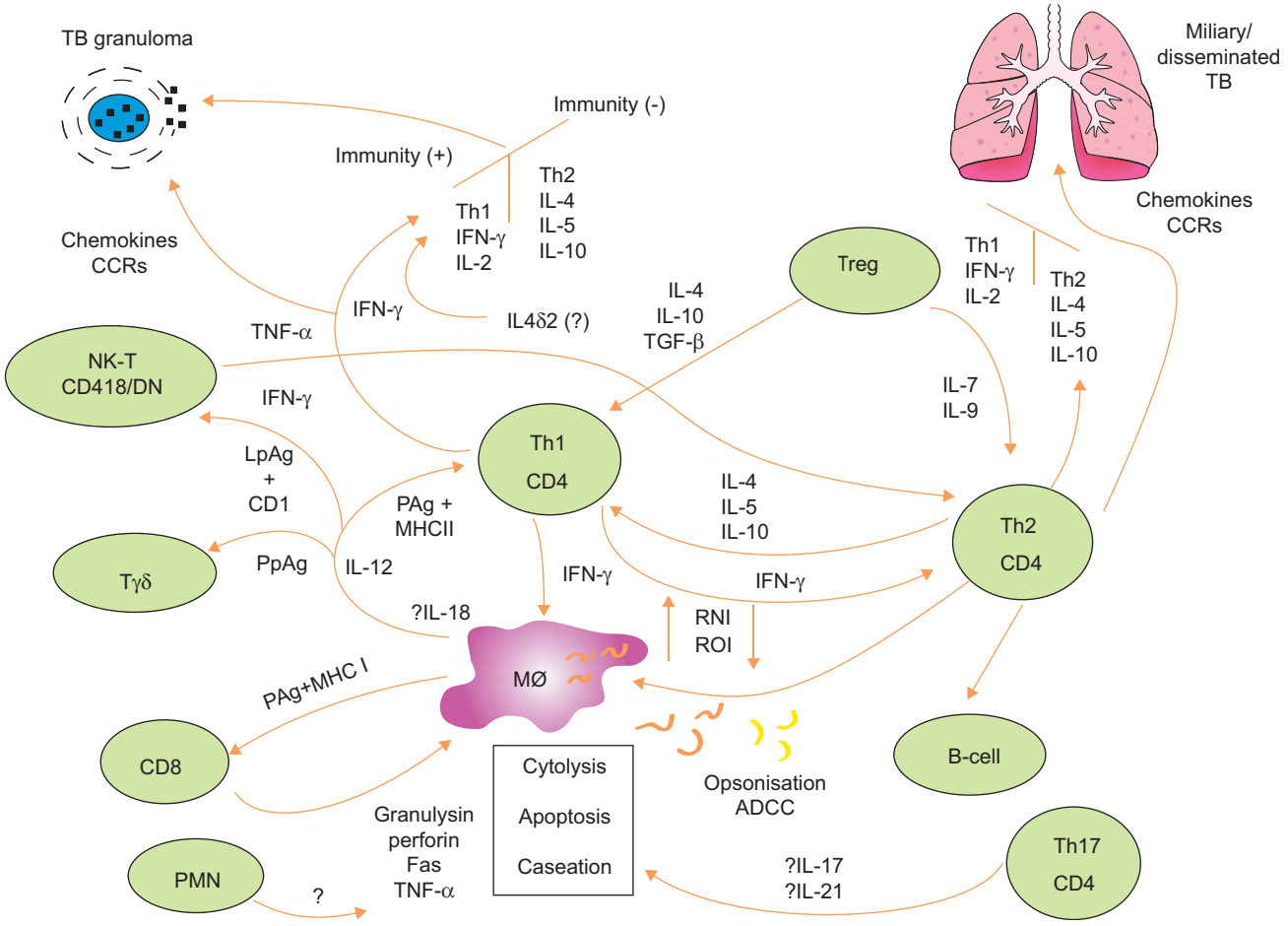

FIGURE 2. Immunopathogenesis of tuberculosis. ADCC: antibody-dependent cell-mediated cytotoxicity; CCR: CC chemokine receptor; DN: double negative; Fas: cell receptor inducing apoptosis; IFN: interferon; IL: interleukin; LpAg: lipopolysaccharide antigen; MØ: macrophage; MHC: major histocompatibility complex antigen; NK: natural killer cell; PAg: peptide antigen; PpAg: phospho-antigen; PMN: polymorphonuclear neutrophil; RNI: reactive nitrogen intermediates; ROI: reactive oxygen intermediates; TB: tuberculosis; TGF: transforming growth factor; Th: T-helper cell; TNF: tumour necrosis factor; Treg: T-regulatory cell.

problems and empyema. Other complications include wound and other infections, bleeding, cardiovascular embarrassment, atelectasis and recurrent laryngeal nerve injury. The risk factors for bronchopleural fistula mainly include sputum-smear positivity, low forced expiratory volume in 1 s, old age, and perhaps the technique of stump closure and reinforcement [230]. There have been no randomised controlled studies that compared bronchial stump reinforcement *versus* nothing or stapling *versus* suturing as a means of closure of the stump. Many authorities, however, have recommended reinforcement of the bronchial stump, especially in selected patients at risk from such complications [222, 230].

In some frail patients with MDR tuberculosis, who usually have limited cardiopulmonary reserve and, thus, would not withstand lung resection, collapse therapy using thoracoplasty [231], plombage [232] and artificial pneumothorax [233] can be considered. Thoracoplasty, aside from causing cosmetically unappealing deformity of the thoracic cage, can be associated with obstructive and restrictive lung function defects after the procedure. Extrapleural lucite sphere plombage can give rise to pressure effects, migration and foreign-body irritation problems. The use of artificial pneumothorax has been reappraised in a recent study with rather encouraging radiographic and bacteriological results [233]. In the intervention group, culture negativity was achieved in all new cases and 81.1% of retreatment cases (~80% of the patients had MDR tuberculosis). Cavity closure occurred in 94.6% and 67.9%, respectively. In the control group, culture negativity was achieved in 70.9% and 40.0%, respectively, and cavity closure occurred in 56.3% and 24.0% respectively.

ADJUNCTIVE IMMUNOTHERAPY IN TUBERCULOSIS

Macrophages, dendritic cells, natural killer cells, γδT-cells and CD1-restricted T-cells are involved in the initial cell-mediated immune response to *M. tuberculosis*, and determine the local or distant progression of infection to disease *versus* containment of the infection. Antigens of *M. tuberculosis* are processed by the antigen-presenting cells. Subsequently, CD4+ cells are involved. T-helper (Th) cells, largely CD4+ cells, generally mature into two functionally different phenotypes, often termed Th1 and Th2 cells. The former secrete principally interleukin (IL)-2 and interferon (IFN)-γ, while the latter largely secrete or induce IL-4, -5, -6 and -10. IL-12 produced by macrophages expands Th1 cell population and upregulates its functions. Cell-mediated protective immunity appears to be

TABLE 6 Preliminary studies on adjunctive immunotherapy of multidrug-resistant tuberculosis

First author [ref.]	Immunomodulator/cytokine	Outcome
CONDOS [246]	IFN-γ (aerosolised)	Bacillary load lowering, radiographic improvement (CT)
JOHNSON [247]	rhuIL-2 (subcutaneous)	Reduced bacillary load, radiographic improvement
PALMERO [248]	rIFN-α2b (subcutaneous)	Bacillary load reduction
GIOSUE [249]	IFN-α (aerosolised)	Bacillary load reduction, radiographic improvement (CT)
GRAHMANN [250]	IFN-γ (aerosolised)	Bacillary load lowering, radiographic improvement
PARK [251]	IFN-γ (subcutaneous)	No bacteriological conversion on smear and culture, no radiographic improvement (CT)
STANFORD [252]	*Mycobacterium vaccae* (intradermal)	Disease ⩽2 yr: cure rate 82% (1–2 doses); chronic cases: cure rates 7.6% (1 dose), 37.9% (7 doses), 41.6% (12 doses)

IFN: interferon; CT: computed tomography; r: recombinant; hu: human; IL: interleukin.

associated with a Th1 response [234]. IL-18, another cytokine linked to Th1 pathway, may also have a putative role in cell-mediated protection against mycobacterial infection [235]. Tumour necrosis factor (TNF)-α, released largely from macrophages, contributes to protecting the host by promoting granuloma formation [236]. However, TNF-α can also cause tissue necrosis under subversive T-cell influence. There is some evidence this sabotage effect comes from IL-4 overactivity [237]. Figure 2 summarises the immunopathogenesis of tuberculosis. Thus, the complex immunopathogenesis of tuberculosis embraces host tissue inflammation and damage, in addition to protective immunity against the tubercle bacilli.

Athough a recent in-depth review on the immunotherapy for tuberculosis has revealed a number of potentially useful agents for immunoregulation, immunoaugmentation or immunosuppression, no evidence-based recommendation can yet be formulated regarding their clinical utility [238].

Adjunctive corticosteroids have been used as an attempt to ameliorate inflammation. Cochrane reviews have shown improved mortality of patients with tuberculous pericarditis [239] and meningitis [240] with steroid therapy, but inconclusive effects for pericardial constriction. Neurological deficit or disability was improved among survivors with tuberculous meningitis. There is currently inadequate evidence on whether steroids are effective in tuberculous pleural effusion [241]. In HIV-infected patients, steroids have been shown to be beneficial in tuberculous meningitis, although the overall prognosis is still poor [242]. Steroid use in tuberculous pleural effusion in HIV-infected patients was associated with a higher incidence of Kaposi's sarcoma [243]. An additional concern is that adjuvant steroid therapy of HIV-related tuberculosis has been associated with a transient increase in viral load [244]. In these two latter studies, the dosages of prednisolone used were 50 $mg \cdot day^{-1}$ and 2.75 $mg \cdot kg^{-1} \cdot day^{-1}$, respectively, with gradual tapering off in 8 weeks [243, 244].

Cytokine supplementation was initially thought to be promising adjunctive therapy in tuberculosis [245], including drug-resistant forms. Table 6 depicts the results of a number of preliminary studies regarding the use of cytokines (especially IFN-γ) [246–251] and *Mycobacterium vaccae* (NCTC 11659) [252], an avirulent vaccine from a nontuberculous mycobacterial species, in the management of MDR tuberculosis. In a more recent study, nebulised IFN-γ1b adjuvant therapy was also found to improve constitutional symptoms, reduce inflammatory cytokines in bronchoalveolar lavage and improve clearance of acid-fast bacilli from sputum in cavitary pulmonary tuberculosis [253]. While the results from some of these studies are encouraging, the limited number of enrolled patients, alongside often uncontrolled experimental designs, leaves great uncertainty regarding the definitive role of these cytokines and allied forms of immunotherapy in tuberculosis treatment.

By enhancing mycobacterial killing in macrophages, vitamin D might have the potential to enable shortening of treatment duration for tuberculosis, reducing infectiousness and improving response in drug-resistant forms of the disease [254]. However, a double-blind, randomised, placebo-controlled trial [255] has recently shown that vitamin D, as a supplementary therapy, did not improve clinical outcome (as assessed by clinical score severity and sputum smear conversion) among patients with tuberculosis. There was also no overall effect on tuberculosis mortality at 12 months. One caveat might be the possibly insufficient dose of vitamin D used. The clinical role of vitamin D in immunotherapy of tuberculosis is currently uncertain.

In addition, there appear to be some agents that can promote intracellular killing of *M. tuberculosis* by macrophages, through affecting the transport of K^+ and Ca^{2+} from the phagolysosome, thereby resulting in better acidification and activation of hydrolases [256]. This might be a promising direction of developing therapy for drug-resistant tuberculosis.

CONCLUSION

In 2010, the prevailing challenges of HIV infection and drug resistance still undermine the global control of tuberculosis. With clear indications that XDR tuberculosis results from mismanaged cases of drug-susceptible and MDR tuberculosis, it is imperative to treat drug-susceptible tuberculosis appropriately to completion, and to provide rapid diagnosis, and aggressive as well as appropriate treatment of MDR tuberculosis to avoid the unnecessary development of additional cases of XDR tuberculosis. The main priority interventions would be: 1) strengthening control of tuberculosis, through sound implementation of the Stop TB Strategy, with special focus on laboratory capacities and infection control (including HIV

TABLE 7 Grading of evidences for recommendations according to the Scottish Intercollegiate Guidelines Network

Study rating	Study design	Requirements	Target population	Grades of recommendation
1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias	⩾1 study	Directly applicable	A
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias	Studies with overall consistency	Directly applicable	A
1++/**1**+	As above	Studies with overall consistency	Extrapolated	B
2++	High-quality case–control/cohort studies or their systemic reviews, with very low risk of confounding/bias and high probability of causal relationship	Studies with overall consistency	Directly applicable Extrapolated	B C
2+	Well-conducted case–control/cohort studies with low risk of confounding/bias and a moderate probability of causal relationship	Studies with overall consistency	Directly applicable Extrapolated	C D
3	Nonanalytic studies, *e.g.* case reports, case series			
4	Expert opinion			

RCT: randomised controlled trial.

control); 2) improvement of programmatic management of drug-resistant tuberculosis, based on updated guidelines, largely from WHO; and 3) promotion of research and development of new diagnostics, vaccines and drugs, as well as other modalities of therapy.

While scientific advancement is crucial to better the care of tuberculosis patients and is earnestly awaited, existing tools must be harnessed in sound public health settings to curb the epidemic of tuberculosis today [257].

APPENDIX

For Appendix, see table 7.

STATEMENT OF INTEREST

None declared.

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