Review

Programmes and principles in treatment of multidrug-resistant tuberculosis

Joia S Mukherjee, Michael L Rich, Adrienne R Socci, J Keith Joseph, Felix Alcántara Virú, Sonya S Shin, Jennifer J Furin, Mercedes C Becerra, Donna J Barry, Jim Yong Kim, Jaime Bayona, Paul Farmer, Mary C Smith Fawzi, Kwonjune J Seung

Multidrug-resistant tuberculosis (MDR-TB) presents an increasing threat to global tuberculosis control. Many crucial management issues in MDR-TB treatment remain unanswered. We reviewed the existing scientific research on MDR-TB treatment, which consists entirely of retrospective cohort studies. Although direct comparisons of these studies are impossible, some insights can be gained: MDR-TB can and should be addressed therapeutically in resource-poor settings; starting of treatment early is crucial; aggressive treatment regimens and high-end dosing are recommended given the lower potency of second-line antituberculosis drugs; and strategies to improve treatment adherence, such as directly observed therapy, should be used. Opportunities to treat MDR-TB in developing countries are now possible through the Global Fund to Fight AIDS, TB, and Malaria, and the Green Light Committee for Access to Second-line Anti-tuberculosis Drugs. As treatment of MDR-TB becomes increasingly available in resource-poor areas, where it is needed most, further clinical and operational research is urgently needed to guide clinicians in the management of this disease.

Mycobacterium tuberculosis has re-emerged as a major public-health threat. Instead of being eradicated, drug-resistant strains have evolved and have been documented in every country surveyed.[1,2] Once a strain of *M tuberculosis* develops resistance to isoniazid and rifampicin, it is defined as multidrug-resistant tuberculosis (MDR-TB). Without these two potent drugs, the treatment of MDR-TB becomes difficult since second-line drugs must be used, which are less potent and not as well tolerated as first-line agents. The improper management of MDR-TB can result in further drug resistance. Patients with MDR-TB frequently have advanced disease associated with thick-walled cavities and chronic lung lesions that can be difficult for antibiotics to penetrate. Therefore they are difficult to cure and pose a substantial threat to household contacts and to tuberculosis control efforts. Even in countries with highly developed health-care systems, outbreaks of MDR-TB have proven difficult to manage. During the early 1990s, several well-publicised outbreaks of MDR-TB in US cities were eventually controlled, but at a cost estimated at millions of dollars.[3]

In resource-poor areas, inconsistent drug supply and weak tuberculosis-control infrastructure can lead to a vicious cycle of inadequate treatment, the generation of tuberculosis-drug resistance, and transmission of resistant strains. People who have primary drug resistance and who are infected with a strain of tuberculosis that is already resistant frequently fail treatment with drug regimens designed for use against drug sensitive disease and become progressively more resistant and difficult to cure.[4] Some countries have already been labelled MDR-TB hot spots, where a substantial proportion of incident tuberculosis is MDR-TB.[1] In areas with a concurrent rising incidence of HIV-1 infection, the prospect of a so-called noxious synergy looms.[5] Opportunities to treat MDR-TB in developing countries are now possible through the Global Fund to Fight AIDS, TB, and Malaria, and the Green Light Committee for Access to Second-line Anti-tuberculosis Drugs.[6,7] The development of evidence-based guidelines for the treatment of MDR-TB is necessary to guide clinicians and programmes throughout the world, particularly in an era of the HIV epidemic, globalisation, and increasing air travel.[8]

The existing data on MDR-TB treatment come entirely from retrospective cohort analyses. These analyses have been cited in policy and modelling reports. However, the non-standard methods of collection and analysis of outcome data do not allow easy comparison. We present a critical overview of studies of MDR-TB treatment, with an emphasis on differences in treatment settings, cohort selection criteria, patients' characteristics, and treatment protocols. Although direct comparisons between these studies are impossible, we have been able to make insights into the treatment of MDR-TB. Most importantly, we underscore the need for further clinical and operational research on MDR-TB treatment.

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Brigham and Women's Hospital, Division of Social Medicine and Health Inequalities, Boston, MA, USA (J S Mukherjee MD, M L Rich MD, J K Joseph MD, S S Shin MD, J Y Kim MD, P Farmer MD, K J Seung MD)**; Partners In Health, Boston, MA, USA** (J S Mukherjee, M L Rich, A R Socci BA, J K Joseph, S S Shin, J J Furin MD, M C Becerra ScD, D J Barry NP, J Y Kim, J Bayona MD, P Farmer, M C Smith Fawzi ScD, K J Seung)**; and Socios En Salud, Carabayllo, Lima, Perú** (J S Mukherjee, M L Rich, J K Joseph, F Alcántara Virú MD, S S Shin, J J Furin, M C Becerra, J Y Kim, J Bayona, P Farmer, K J Seung)

Correspondence to: Dr Joia S Mukherjee, Program in Infectious Disease and Social Change, Department of Social Medicine, Harvard Medical School, 641 Huntington Avenue, Boston, MA 02115, USA (e-mail: jmukherjee@pih.org)

Search strategy

We searched MEDLINE from 1966 to 2001 and BIOSYS from 1970 to 2001, with use of the following key words: MDR-TB, multidrug-resistant tuberculosis, rifampin resistance, isoniazid resistance, tuberculosis, drug resistance, treatment, DOTS, and outcomes. We also searched the bibliographies of articles for relevant references.

Cohort number: study and setting	Time since tuberculosis diagnosis (years)	Drug susceptibility testing	Treatment	Treatment regimens	Comments
1: Viskum, et al,[9] referral hospital, Copenhagen, Denmark (n=8)	Unknown	BACTEC testing of first-line and second-line drugs	Previous tuberculosis treatment in 88%. Mean 4·3 drugs used, mean 4·8 resistant. Mean duration 13 months, with 100% cure rate and 0/8 relapses.*† Resective surgery use unknown No outpatient DOT	Z, OFX, CS, injectable (S, AMK) used in all patients; PAS and thiacetazone used in one patient each; injectable agent administered for 3–12 months	All cases in Denmark 1993–95; all patients tested negative for HIV-1 infection
2: Geerligs, et al,[10] two referral hospitals, Netherlands (n=39)	Unknown	Modified absolute concentration method on 7H10; first-line and second-line drugs, including Z	Previous tuberculosis treatment in 34%. Mean 6 drugs used, mean 5 resistant. Mean duration 20 months, with 95% cure rate, 5% deaths, and 3/44 relapses.*† Resective surgery used in 6 patients No outpatient DOT	Used in >80% of patients: H, E, Z, injectable (S, KM, AMK), quinolone (CPX or OFX), CFZ	Only patients with risk factors for HIV-1 infection tested, and all negative
3: Telzak, et al,[11] seven hospitals, New York, NY, USA (n=16)	2·5 (median)	Varied by hospital; BACTEC and solid media used; first-line and second-line drugs	Previous tuberculosis treatment in 32%. Mean 4·1 drugs used, mean 3·4 resistant. Median duration 18 months, with 81% cure rate and 19% default rate. Relapses unknown. Resective surgery used in 3 patients No outpatient DOT	Quinolone (OFX, CPX) used in all patients; injectable (SM, KM, AMK, CM) used in >80% of patients	Cases identified through network of hospital-based physicians; all patients tested negative for HIV-1 infection
4: Narita, et al,[12] referral hospital, FL, USA (n=39)	Unknown	BACTEC testing of all first-line and some second-line drugs; 7H11 media used for some second-line drugs	Previous tuberculosis treatment unknown. Mean 5·5 drugs used, mean 6·6 resistant. Mean duration 18 months, with 79% cure rate, 3% default rate, and 18% death rate. Relapses unknown. DOT used. Resective surgery used in 5 patients		Cohorts 4 and 13 originally reported as part of same study; cohort received treatment at specialised tuberculosis treatment centre; 41% HIV-1 positive
5: Tahaoğlu, et al,[13] referral hospital, Istanbul, Turkey (n=158)	6·7 (mean)	Proportion method on L-J; tested H, R, E, S	Previous tuberculosis treatment in 78%. Mean 5·5 drugs used, mean 4·4 resistant. Mean duration >18 months after last positive culture, with 75% cure rate* 8% failure rate, 11% default rate, 5% death rate, and 1/88 relapses. Resective surgery used in 36 patients No outpatient DOT	General protocol: injectable (S, KM, AMK, CM) plus >2 oral agents; used in >80% of patients: OFX, PTH, CS	All patients tested negative for HIV-1 infection
6: Avendaño, et al,[14] referral hospital, Toronto, Canada (n=32)	Unknown	BACTEC testing of first-line and second-line drugs	Previous tuberculosis treatment in 60%. Mean number of drugs used unknown, mean 3·9 resistant. Mean duration 24 months, with 75% cure rate, 3% failure rate, 6% default rate, 16% death rate, and 4/24 relapses. Some DOT used. Resective surgery used in 6 patients	General protocol: injectable, quinolone, CFZ plus other oral drugs; used in >80% of patients: a quinolone (CPX, OFX, LVX), CFZ	All patients tested negative for HIV-1 infection
7: Mitnick, et al,[15] walk-in clinic programme, Peru (n=75)	3·7 (median)	Proportion method on L-J; first-line and second-line drugs; BACTEC for Z	Previous tuberculosis treatment in 100%. Median 6 drugs used, median 6 resistant. Median duration 23 months, with 73% cure rate, 1% failure rate, 7% default rate, 19% death rate, and 1/75 relapses. DOT used.*† Resective surgery used in 3 patients No outpatients DOT	Used in >80% of patients: injectable (S, KM, AMK, CM), quinolone (OFX, CPX), CS, PAS; injectable continued until 6 months of negative cultures	1/65 patients tested positive for HIV-1 infection
8: Yew, et al,[16] referral hospital, Hong Kong (n=75)	6·7 (mean)	Resistance ratio method on L-J; first-line and second-line drugs, including Z	Previous tuberculosis treatment in 65%. *Mean 4·7 drugs used, mean 3·5 resistant. Mean duration 14·4 months, with 69% cure rate, 9% failure rate, 13% default rate, 8% death rate, and 1/47 relapses. DOT used. Resective surgery use unknown	96% received quinolone (OFX, LFX); injectable (S, KM, AMK) administered for 3–6 months	All patients tested negative for HIV-1 infection
9: Park, et al,[17] referral hospital, South Korea (n=107)	Unknown	Proportion method on L-J; first-line and second-line drugs; Wayne method	Previous tuberculosis treatment in 100%. Mean 5·1 drugs used, mean 4·2 resistant. Mean duration >24 months after last positive culture, with 68% cure rate, 11% failure rate, 20% default rate, 0/52 relapses.*† Resective surgery used in 22 patients. No outpatient DOT	General protocol: injectable (S, KM) plus 4 oral drugs; injectable administered for 6 months	Cases identified by reviewing patients' records at walk-in clinic; all patients tested negative for HIV-1 infection
10: Goble, et al,[18] referral hospital, Denver, CO, USA (n=167)	6·0 (median)	Proportion method on 7H11; first- line and second-line drugs; Wayne method	Previous tuberculosis treatment in 100%. Median 4 drugs used, median 6 resistant. Mean duration >24 months after last positive culture, with 49% cure rate, <32% failure rate, 14% default rate, >5% death rate, and 3/78 relapses.*† Resective surgery used in 7 patients No outpatient DOT	General protocol: injectable (S, KM, AMK, CM, VM) plus >2 oral drugs; injectable given for 4–6 months after culture conversion; quinolones not used	Patients first seen between 1973 and 1983, so few likely to be infected with HIV-1
11: Kim et al,[19] walk-in clinic, South Korea (n=1011)	6·4 (mean)	Proportion method on L-J; first-line and second-line drugs; Wayne method	Previous tuberculosis treatment in 100%. Mean 5·3 drugs used, mean 3·7 resistant. Mean duration 23 months, with 48% cure rate, 8% failure rate, 39% default rate, 5% transfer out, 0·3% death rate, and 8/335 relapses. Resective surgery use unknown No outpatient DOT	General protocol: injectable (S, KM, VM) plus 4 or 5 oral drugs	Patients previously treated with second-line drugs excluded from analysis; HIV-1 testing not done

(continues)

Cohort number: study and setting	Time since tuberculosis diagnosis (years)	Drug susceptibility testing	Treatment	Treatment regimens	Comments
12: Suarez,et al,[20] walk-in clinic programme, Peru (n=466)	Unknown	DST done in some cases but not used to change treatment	Previous tuberculosis treatment in 100%. Mean 5 drugs used, mean resistant unknown. Mean duration 18 months, with 48% cure rate, 28% failure rate, 11% default rate, and 12% death rate. Relapses unknown. DOT used. Resective surgery use unknown	Standard empirical regimen used in all patients: E, Z, KM (3 months), CPX and ETH	Most patients previously treated with WHO category 1 or 2 regimens; HIV-1 testing not reported
13: Narita et al,[12] ambulatory patients in FL, USA (n=39)	Unknown	BACTEC testing of all first-line and some second-line drugs; 7H11 media used for some second-line drugs	Previous tuberculosis treatment unknown. Mean 2·87 drugs used, mean 3·23 resistant. Mean duration unknown. 38% cure rate, 21% default rate, 41% death rate. Relapses unknown. Some DOT used. Resective surgery use unknown		Cohorts 4 and 13 originally reported as part of same study; cohort received treatment from Health Department and local private physicians; 48% HIV-1 positive

Z=pyrazinamide. OFX=ofloxacin. CS=cycloserine. S=streptomycin. AMK=amikacin. PAS=paraminosalicylic. H=isoniazid. R=rifampicin. E=ethambutol. KM=kanamycin. CPX=ciprofloxacin. CFZ=clofazamine. DOT=directly observed treatment. CM=capreomycin. PTH=prothionamide. LVX=levofloxacin. L-J=Lowestein-Jensen agar. VM=viomycin. DST=drug sensitivity testing. ETH=ethionomide. *Personal communication. †Number of reported relapses per number of patients who received post-treatment follow-up.

Table 1: **Treatment-outcome studies of MDR-TB**

Cohort studies

Selection of studies

We included studies if patients were treated for MDR-TB with second-line drugs; treatment regimens were documented; and, cure, death, default (treatment suspension), treatment failure, and relapse rates were reported or could be obtained by contacting the original researchers. Because we sought to assess the treatment of MDR-TB separately from the interaction between HIV-1 and tuberculosis infection, we excluded studies if the HIV-1 prevalence in the cohort was higher than 50%. The following information was extracted: length of illness due to tuberculosis, history of previous tuberculosis treatment, antituberculosis drugs to which strains were resistant, number of drugs used in treatment regimen, duration of treatment, HIV status, use of surgery, and demographic data. We contacted the reports' researchers to obtain missing information.

Table 1 shows the 13 retrospective cohort analyses from 12 studies we identified published from 1993 to 2003.[9–20] We know of no clinical trial in which any feature of MDR-TB treatment has been assessed. The median number of patients who started MDR-TB treatment in each cohort was 75 (range 8–1011). We excluded patients who died or stopped treatment through non-adherence before an appropriate regimen was started. Only two cohorts (4 and 13) had a notable number of HIV-1-positive patients; in all other cohorts, HIV-1 co-infection was minimal or not routinely tested.

Most studies were done in developed countries: Denmark, Netherlands, USA, Canada, Hong Kong, and South Korea. Two were done in low-income or middle-income countries—Peru and Turkey. Nine cohorts were treated at tertiary referral hospitals, and four in outpatient clinics. The most common method of retrospectively constructing cohorts of MDR-TB patients was to use laboratory records to identify strains with resistance to isoniazid and rifampicin. In some cohorts, however, other sampling techniques were reported. Cohort 3 was made up of patients identified through a specific referral network of hospital physicians. In cohort 9, cases of MDR-TB were identified by reviewing clinic records, even though most patients had previously been admitted to the hospital for several months to start treatment with second-line drugs. In cohort 11, MDR-TB patients who had previously been treated with second-line drugs were excluded from analysis. Patients in cohort 12 were selected for treatment with a standard regimen for MDR-TB on the basis of previous treatment failure on short-course chemotherapy without confirmation of resistance to isoniazid and rifampicin.

Treatment regimens

In all cohorts except cohort 12, treatment regimens were individually tailored to drug susceptibility testing (DST) results and previous treatment history. There was no standard method of choosing which drugs to use in the treatment regimens; however, an injectable agent (an aminoglycoside or capreomycin) and a quinolone formed the core of all regimens except for that in the earliest study, cohort 10, which predated the routine use of quinolones for the treatment of MDR-TB. Cohort 12 was the only cohort in which DST was not used to tailor regimens; every patient in the cohort received the same regimen of ethambutol, pyrazinamide, kanamycin, ciprofloxacin, and ethionamide, irrespective of DST. Different methods were used to calculate the mean or median numbers of drugs reportedly taken. For example, in cohort 8 the mean number of drugs taken by patients at the beginning of the treatment period was reported; in cohort 7 the median number of drugs taken for longer than 1 month at any time during the entire treatment period was reported. In addition, sensitivity documented by DST was not proven for every drug used in a given regimen. The researchers for cohort 2 stated that they frequently used isoniazid even though all infecting strains had documented resistance to the drug. In cohorts 7 and 9, second-line drugs to which strains had documented resistance were occasionally used to treat highly resistant cases. Only in cohorts 5, 8, 9, 10, 11, and 12 were the actual doses of the drugs used reported, and doses varied substantially between studies.

Number of resistant drugs and drug susceptibility testing

The reported mean or median number of drugs to which isolates were resistant ranged from 3·2 to 6·6. Studies did not test susceptibility to the same number of drugs. In cohorts 5 and 12, only DST to first-line antituberculosis drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) was done. Patients in cohort 12 where treated with an empirical MDR-TB regimen and not all patients received DST. Of the 72% of patients who

received DST, 87% had documented resistance to isoniazid and rifampicin.

Studies reported a range of DST methods, with use of solid and liquid media; some non-standard methods were reported. In cohorts 1, 4, 6, and 13, the proprietary liquid media system BACTEC (Becton, Dickinson, and Company of Franklin Lakes, NJ, USA) was used to test first-line and second-line drugs. Pyrazinamide testing, when available, was mainly done with the Wayne method; in later studies, BACTEC testing became more common.

Treatment outcomes

The mean or median duration of treatment was reported for cohorts 1, 2, 3, 4, 6, 7, 8, and 11, and ranged from 13 to 24 months. The shortest lengths of treatment were reported in Denmark (cohort 1) and Hong Kong (cohort 8). When criteria for successful treatment were reported, these criteria generally stipulated 18–24 months of chemotherapy after the last positive culture.

In cohorts 4, 6, 7, 8, 12, and 13, directly observed treatment was used, but in only four (4, 7, 8, and 12) was it for the entire duration of treatment. An additional six cohorts (1, 2, 3, 5, 9, and 10) were treated as inpatients at the beginning of treatment, at which time treatment was observed or closely monitored; after discharge, treatment was self-administered.

We made every effort to assess treatment outcomes across studies in a standard way. Since treatment outcomes were reported according to various definitions in the original studies, we recalculated the published treatment outcome data with additional information obtained from the researchers to reflect four consistent and mutually exclusive outcomes: cure, failure, death, and default.[21] Reported cure rates were revised in many studies after including patients lost to follow-up. The recalculation of treatment outcomes, although helpful in the comparison of these studies, does not correct for more fundamental differences in cohort characteristics produced by the differences in practices for referral of patients and cohort selection criteria.

The most common definition of cure was the completion of a prescribed course of treatment with 12 or more months of negative cultures (cohorts 3, 4, 5, 6, 7, 9, 10, and 13). In cohort 8, cure was defined as 6 months of consistently negative cultures. In cohort 11, cure was defined as two or more negative cultures at the end of treatment. In cohort 12, cure was defined as two negative smears or two negative cultures at the end of the 18-month treatment period. In cohorts 1 and 2, the definition of cure was not stated. Failure was defined as the occurrence of persistently positive sputum despite treatment. Death was defined as all causes of death during treatment. We defined default as treatment suspension for any reason. Relapse was only reported in a few studies but we included it after obtaining information from the original researchers. Relapse was defined as a positive culture during the follow-up period after documented cure.

Treatment outcomes for each cohort are listed in table 1. Cure rates ranged from 38% (cohort 13) to 100% (cohort 1). Default rates ranged from 0% (cohorts 1 and 2) to 44% (cohort 11), although the latter included a transfer rate of 4·5%.

	Efficacy against *M tuberculosis*
Group 1: Oral first-line agents	
Isoniazid, rifampicin, pyrazinamide, ethambutol	In-vitro and in-vivo clinical data support use. Historical and clinical evidence suggests that these agents are most potent oral antituberculosis medications. Ethambutol is generally bacteriostatic, but at high doses (25 mg/kg) can be bactericidal.[24] In-vitro and in-vivo clinical data support use
Group 2: Injectables	
Streptomycin, kanamycin, amikacin, capreomycin	Bactericidal. In-vitro and in-vivo clinical data support use[25–28,29]
Group 3: Fluoroquinolones	
Ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin, sparfloxacin	Bactericidal. In-vitro and in-vivo clinical data support use.[30–32] Newer agents (moxifloxacin, gatifloxacin, sparfloxacin) have lower minimum inhibitory concentrations,[33,34] but clinical importance of this feature unknown
Group 4: Bacteriostatic second-line drugs	
Ethionamide, cycloserine, P-aminosalicylic acid	Bacteriostatic. In-vitro and in-vivo clinical data support use[26–29,35–39]
Group 5: Other drugs (potentially useful agents with conflicting animal or clinical evidence or agents with unclear efficacy because of possible cross-resistance)	
Clofazimine	Bacteriostatic in vitro.[40] Conflicting animal model data. MIC90 <1·0 mg in vitro. Concentrations attainable in vivo, particularly in macrophages.[41,42] Activity in murine and guinea pig models, but no activity in rhesus monkey model[43] (between-species differences may be explained by peak serum differences)[44]
Amoxicillin/clavulanic acid	β lactams in combination with b lactamase inhibitors bactericidal in vitro.[45] Conflicting clinical data of early bactericidal activity. One report showed significant decrease in colony-forming units when used alone for 7 days[46] and suggests possible role,[47] whereas another showed no effect[48]
Clarithromycin	Although in-vitro antimycobacterial properties reported,[49,50] including increase in ability when used in combination with standard antituberculosis drugs against multidrug-resistant strains, data from animal and in vivo studies conflicting.[28,51–53] Clinical usefulness remains to be determined
Rifabutin	May be useful against some isolates of MDR-TB (resistant to rifampicin in vitro but sensitive to rifabutin). Clinical experience suggests no role in routine use in treatment of MDR-TB because of cross-resistance with rifampicin[32,54–56]
Thiacetazone	In-vivo and in-vitro evidence of bacteriostatic activity. Cross-resistance frequently seen between thiacetazone and both isoniazid and ethionamide. High rate of side-effects in HIV-1 patients; use not recommended in patients with suspected HIV-1 infection[57–59]
High-dose isoniazid	Animal model supports use. Conflicting clinical data. Cessation of INH generally recommended in confirmed MDR-TB, however high doses (16–20 mg/kg twice weekly) might have a role.[60,61] In one study, regular doses of no benefit.[61] Supporting data in a mouse model[62]

Potency of drugs decreases from top to bottom of table.

Table 2: **Hierarchy of classes of antituberculosis drugs and evidence for use**

Other treatment

The proportion of patients who had a history of treatment for tuberculosis ranged from 32–100%. In several studies patients were reported as being referred for treatment only after failing to respond to other treatment regimens. Cohorts 2 and 3 had the lowest proportion of re-treatment cases at 34% and 32%, respectively. Among patients with history of tuberculosis, the length of time with tuberculosis ranged from 2·5 to 6·7 years.

Adjunctive resective surgery was reportedly used in cohorts 2, 3, 4, 5, 6, 7, 9, and 10. The proportion of patients that received surgery in these cohorts ranged from 4–23%.

Treatment in resource-poor areas

In areas with poor socioeconomic conditions where access to tertiary care is limited, it would be hard to treat cases of MDR-TB only in specialised centres. Our review shows that, importantly, MDR-TB treatment is feasible in a wide variety of settings. In several studies MDR-TB treatment was provided to large numbers of MDR-TB patients in outpatient treatment centres in resource-poor areas.

In the past, MDR-TB has been deemed too expensive to treat patients in low-income countries. The price reduction of second-line drugs, however, has made treatment more affordable. In cohort 12, a cost-effectiveness analysis was done. Although this study had a low cure rate (48%), the researchers concluded that treating MDR-TB with second-line drugs is feasible and cost effective. The cost per disability-adjusted life year saved was US$211, and the average total treatment cost per patient was $2381. The cost per disability-adjusted life year saved is lower than the per-person gross domestic product of many countries, a general benchmark for assessing whether or not an intervention is cost effective.[22] Such values are low enough to be judged by the World Bank as reasonable investments even in low-income countries.

With new funding opportunities for MDR-TB, treatment from the Global Fund to Fight AIDS, TB, and Malaria, and further reductions in the prices of second-line tuberculosis drugs, increased variation in treatment settings and numbers of MDR-TB patients can be expected in the future. Evidence-based clinical guidelines for MDR-TB treatment are urgently needed, for specialty centres and for resource-poor outpatient treatment centres that will treat the largest number of patients with MDR-TB. The studies we reviewed do not answer many crucial questions about how best to treat MDR-TB since differences in baseline cohort characteristics and treatment settings make direct comparison impossible. However, some insights about MDR-TB treatment may be learned from a careful review of the existing scientific evidence.

When to treat and drug regimens

The starting of treatment early is crucial to the effective treatment of MDR-TB. In many studies, 100% of patients had previously failed to respond to treatment for tuberculosis. Cohorts 2 and 3 had the greatest proportion of treatment-naive patients and were among the studies with the highest cure rates. Delay in the diagnosis of MDR-TB results in patients presenting with chronic disease, progressive parenchymal destruction, higher bacillary loads, and continuing transmission.[23,24] Although rapid diagnostic tools such as BACTEC might not be available in resource-poor settings, every effort should be made to quickly identify patients with MDR-TB and start effective treatment.

In the studies we reviewed, drug regimens were frequently individually tailored to DST results. Although the use of empirical regimens, in which patients are given a standard combination of second line drugs based on their likely pattern of resistance, has been suggested if DST is unavailable or unreliable, the practical usefulness of this approach has not been validated in controlled trials. Only cohort 12 used a fully empirical approach to MDR-TB treatment, although the cure rate was poor. On the other hand, cohort 5 was treated with a partly empirical approach—first-line drugs were selected on the basis of DST, but second-line drugs were selected on the basis of previous treatment history. In this study the cure rate was good (75%), which suggests that at least partly empirical approaches may be effective in some settings.

Second-line antituberculosis drugs should be selected based on efficacy. Table 2 presents the known antituberculosis drugs grouped hierarchically based on the evidence of their efficacy against *Mycobacterium tuberculosis*.[25–68] An injectable agent and a quinolone should be included in any MDR-TB treatment regimen. Treatment regimens in the reviewed cohort studies varied enormously, but all included an injectable aminoglycoside or capreomycin. Quinolones have become indispensable in the treatment of MDR-TB because of their bactericidal activity and excellent oral bioavailability, and were used in all studies except the earliest before quinolones were considered standard of care in the treatment of MDR-TB.

The use of multidrug regimens in the treatment of tuberculosis helps to prevent drug resistance. Poor drug availability, the lack of controlled trials, and provider inexperience, have led to regimens commonly being incorrect or inadequate.[69] The exact number of second-line drugs in an MDR-TB treatment regimen needed to prevent the creation of further drug resistance is unknown. Most studies used regimens of four to six drugs, a prudent approach given the high bacillary burden and chronic lesions among patients and the poor potency and penetration of second-line drugs. If a partly or fully empirical treatment approach is taken, the use of many second-line drugs might be advisable to cover the possibility of pre-existing resistance. The importance of using a sufficient number of drugs in an MDR-TB treatment regimen is highlighted by a subgroup analysis of cohorts 4 and 13 by Narita and colleagues,[12] who argued that patients treated by subspecialists at a tertiary referral centre in Florida, USA, had significantly better treatment outcomes than did those treated in the community, partly because of a significant difference in the mean number of drugs used in the two cohorts (5·51 *vs* 2·87).

We recommend a systematic algorithm for the design of MDR-TB treatment regimens. Based on table 2, a five-drug regimen can be designed (panel) by adding drugs from each of the five groups, to which patient's isolate is sensitive. First-line drugs should be used whenever possible, all regimens should contain an injectable and a quinolone, and the remainder of the five-drug regimen can be comprised of bacteriostatic second-line agents.[70] Given the severity of disease and poor potency of the second-line antituberculosis drugs, high-end dosing of these medications should be used whenever possible.

Aggressive treatment regimens, using four to six drugs to which isolates had documented sensitivity, were frequently used in the cohort studies. The dominant resistance pattern was not to isoniazid and rifampicin alone. The mean or median number of resistant drugs in

most studies was four or more, including ethambutol and pyrazinamide in addition to isoniazid and rifampicin. These highly resistant MDR-TB strains have been documented in resource-poor settings where resistance has developed to four or five drugs because of repeated use of empirical short-course chemotherapy with first-line antituberculosis drugs, a phenomenon termed the amplifier effect.[4,71] Such highly resistant patterns of drug resistance also argue for early initiation of aggressive treatment protocols for MDR-TB.

In the studies we reviewed, default from treatment was an important cause of poor cure rates, particularly in some of the outpatient centre studies. Directly observed treatment and other strategies to support adherence are highly recommended. Adherence is a major problem in the treatment of MDR-TB because of the long duration of treatment and adverse effects of second-line drugs. Chaulk and Kazandjian[72] assessed adherence principles in a review of tuberculosis programmes and showed that treatment completion rates for pulmonary tuberculosis exceeded 90% when treatment included directly observed therapy with multiple incentives to improve adherence to treatment, such as transportation vouchers (enablers) or food supplements (enhancers). DOT also allows for the daily monitoring of adverse effects, the timely management of which may promote adherence.[15] Directly observed treatment will probably become more common for MDR-TB, since it is a standard requirement in WHO's guidelines on the treatment of this disorder.[73] Additional strategies to improve adherence include support groups for patients, education for patients and family, nutritional support, case workers, transportation, and housing assistance.

Recommendations for design of MDR-TB treatment regimen

The individualised treatment is based on DST or drugs thought to be sensitive. Drugs are added until five adequate drugs are found. More than five can be used if a drug's sensitivity is unclear or if the regimen contains few bactericidal drugs.

1. Use any first-line oral agent to which isolate is sensitive. Isoniazid, rifampicin, ethambutol, or pyrazinamide.
2. Use an injectable to which an isolate is sensitive. An aminoglycoside or capreomycin. Injectable agents used for >6 months after culture conversion since frequently one of only two bactericidal components of treatment regimen.
3. Use a quinolone. If isolate resistant to a lower-generation quinolone, but sensitive to higher-generation quinolones, consider use of the latter. Quinolones have been used in randomised controlled trials.
4. Add as many second-line bacteriostatic second line agents as needed to make up the five-drug regimen. Among the second-line agents, ethionamide and cycloserine are generally used first because of efficacy, side-effect profile, and price, shown through in-vivo and in-vitro evidence, and historical use in tuberculosis. P-aminosalicylic acid frequently used in patients with higher-grade resistance.
5. Other drugs.

If regimen does not contain five adequate medications, consider use of additional agents such as amoxicillin or clavulanate and clofazimine, dependent on clinical status, disease burden, degree, and pattern of resistance and other factors.

Improvement of treatment provision

Despite the many challenges in the diagnosis and treatment of MDR-TB, many of the studies we reviewed show that successful treatment is possible in various settings, that aggressive regimens with four to six drugs, attention to adherence, and management of side-effects are important in achieving high cure rates. However, many crucial management issues remain unresolved and cannot be answered through the existing data. The evidence-based treatment recommendations we present, based on the reviewed papers, provide only general guidance to clinicians. Controlled clinical trials are needed to answer more complex questions concerning best treatment regimens and optimum treatment protocols for MDR-TB. In addition, further operational research in resource-poor areas is needed to address common programme issues, such as high treatment default rates. As treatment becomes increasingly available in these settings, where it is needed most, clinical and operational research is urgently needed to guide clinicians worldwide in the management of MDR-TB.

Conflict of interest statement
None declared.

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