Review Article

Multi-Drug Resistant Tuberculosis - An Indian Scenario

Auxilia Hemamalini Tilak[1*], K. C. Supraja[2]

1. Professor & Head, Department of Microbiology, Asan Memorial Dental College & Hospital, Chengalpet, India.
2. Lecturer, Department of Microbiology, Asan Memorial Dental College & Hospital, Chengalpet, India.

Abstract

Tuberculosis remains one of the major public health problems in India. It was estimated that about 30% of the world's tuberculosis patients are residing in India. Multidrug-resistant tuberculosis caused by Mycobacterium tuberculosis resistant to both isoniazid and rifampicin with or without resistance to other drugs is the most worrisome elements of the pandemic of antibiotic resistance. Moreover, patients with HIV infection are known to have a high risk of tuberculosis and the case fatality rate is high among patients with AIDS, infected with strains of drug resistant M. tuberculosis. All measures should be taken to encourage patients not to stop treatment despite all its discomforts to prevent morbidity, mortality and transmission of MDR-TB. Efforts must be focused on the effective use of first line drugs in every new patient so as to prevent the ultimate emergence of multidrug resistance. The use of reserve drugs to cure multi-drug resistant tuberculosis and to reduce further transmission should be considered, but only as part of well structured programme of tuberculosis control. The definitive diagnosis of MDR-TB is difficult in resource poor low income countries because of non-availability of reliable laboratory facilities. Efficiently run tuberculosis control programmes based on directly observed treatment, short-course policy is essential for preventing the emergence of MDR-TB. Management of MDR-TB is a challenge which should be undertaken by experienced clinicians at centres equipped with reliable laboratory service for mycobacterial culture and in vitro sensitivity testing as it requires prolonged use of expensive second-line drugs with a significant potential for toxicity.

Keywords: Antibiotic resistance, Multidrug resistance, HIV, Isoniazid, Pandemic, Rifampicin, Tuberculosis

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Address for Correspondence:
Dr. Auxilia Hemamalini Tilak,
Professor & Head, Department of Microbiology, Asan Memorial Dental College & Hospital, Chengalpet, India.
E mail: suprajachakrapani79@gmail.com

INTRODUCTION

Tuberculosis (TB) is as old as the mankind [1-3]. TB is the most common cause of death due to a single infectious agent worldwide in adults [4]. In 1993, the World Health Organization (WHO) took an unprecedented step and declared TB to be a global emergency [4-6]. According to the recent estimates, one third of the human population (about 1.86 billion people) were infected with *Mycobacterium tuberculosis* worldwide in 19977). TB is principally a disease of poverty, with 95 per cent of cases and 98 per cent of deaths occurring in developing countries.

Of these, more than half the cases occur in five South East Asian countries [7]. In 1997, nearly 1.87 million people died of TB and the global case fatality rate was 23%.

This figure exceeded 50 per cent in some of the African countries where human immunodeficiency virus (HIV) is highly prevalent [7]. The 2016 global TB report is based primarily on data gathered from countries and territories. WHO has implemented annual rounds of global TB data collection since 1996, with an online system[8] used since 2009.Other sources of data used in 2016 include the HIV department in WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS), which collect information about the provision of TB preventive treatment to people living with HIV and about antiretroviral therapy for HIV-positive TB patients; the creditor reporting system of the Organisation for Economic Co-operation

and Development (OECD); the World Bank, for development indicators; and the WHO national health accounts database. This is the first global TB report to be produced in the post-2015 era of the Sustainable Development Goals (SDGs) and the End TB Strategy, which have superseded the Millennium Development Goals (2000–2015) and the Stop TB Strategy (2006–2015), respectively. The SDGs were adopted by the UN in September 2015 and cover the period 2016–2030. The End TB Strategy spans a 20-year timeframe (2016–2035) and was unanimously endorsed by WHO's Member States at the 2014 World Health Assembly. The SDGs and the End TB Strategy share a common aim: to end the global TB epidemic. Targets set in the End TB Strategy include a 90% reduction in TB deaths and an 80% reduction in TB incidence by 2030, compared with 2015.It is estimated that between 2002 and 2020, approximately 1000 million people will be newly infected, over 150 million people will get sick, and 36 million will die of TB if proper control measures are not instituted.

Though the disease was known since ancient times, the organism causing TB was described only a century ago by Robert Koch on 24th March 1882[3]. Until middle of the 20th century, there was no definitive treatment available for TB. With the availability streptomycin, isoniazid and para aminosalicylic acid (PAS), in the mid1940s, predictable, curative treatment for TB became a reality [2]. The introduction of rifampicin, pyrazinamide and ethambutol in the subsequent years ushered in the era of short-course treatment. Further, the fully supervised sanatorium based treatment of the earlier days also gave way to the totally unsupervised domiciliary treatment. Soon, it was felt that TB could be easily contained and possibly eradicated. The advent of HIV infection, the acquired immunodeficiency syndrome (AIDS) pandemic in the 1980s [1,9,10] struck a blow to this optimism and there has been a global resurgence of TB. Strains of *M. tuberculosis* resistant to both isoniazid and rifampicin with or without resistance to other drugs have been termed multidrug-resistant strains. Multidrug-resistant tuberculosis (MDR-TB) is among the most worrisome elements of the pandemic of antibiotic resistance because TB patients that fail treatment have a high risk of death [11-15].

RATIONALE FOR STRICT DEFINITION

Isoniazid, the most powerful mycobactericidal drug available, ensures early sputum conversion and helps in decreasing the transmission of TB. Rifampicin, by its mycobactericidal and sterilising activities is crucial for preventing relapses. Thus, isoniazid and rifampicin are keystone drugs in the management of TB. While resistance to either isoniazid or rifampicin may be managed with other first-line drugs, resistance to both isoniazid and rifampicin (MDR-TB) demands treatment with second-line drugs. These drugs have limited sterilising capacity and are not suitable for short course treatment. Thus, patients with MDR-TB require prolonged treatment with drugs that are less effective and more toxic. Therefore, it is necessary to distinguish MDR-TB from mere drug-resistant tuberculosis by performing mycobacterial culture and sensitivity testing because the therapeutic implications are different.

It is possible to strictly define a given isolate of *M. tuberculosis* as multidrug-resistant only after performing mycobacterial culture and in vitro sensitivity testing. Under programme conditions, these facilities are usually not available and patients are labelled as "treatment failure", "re-treatment failure" and "chronic cases" as per the guidelines issued by the WHO [16]. It is likely that several of these patients may be excreting multidrug-resistant organisms. Keeping these facts in mind, the term MDR-TB has been used in this review in the strict sense of the definition referring to isolates resistant to both isoniazid and rifampicin with or without resistance to other drugs.

DEFINITION

Multi-drug resistant tuberculosis is defined as disease due to *M tuberculosis* that is resistant to Isoniazid (H) and Rifampicin (R), with or without resistance to other drugs. Primary drug resistance is defined as drug resistance in a patient who has not received any anti-tubercular treatment in the past, while acquired drug resistance is defined as resistance that develops in a

patient who has received prior chemotherapy. Recently the terms "resistance in new cases" and "resistance in previously treated cases," have been proposed for use because of the difficulty to confirm the validity of the patients' past history of treatment. When one is not sure whether the resistance is primary or acquired or unaware of patient's previous treatment, drug resistance is known as initial drug resistance.

Certain key definitions concerning clinically important forms of TB, drug-resistant TB are listed in (**Table 1**) [17-35] and (**Table 2**) [29-35] respectively.

Table 1: TB Key Clinical Definitions

TB Suspect
Any person who presents with symptoms or signs suggestive of TB, such as, productive cough for more than 2 wk, which may be accompanied by other respiratory symptoms (e.g., dyspnoea, chest pain, haemoptysis) and/or constitutional symptoms (fever, anorexia, weight loss, fatigue and night sweats).
Case of TB
(i) a "definite case of TB" (vide infra); or (ii) one in whom a medical practitioner has diagnosed TB and has decided to treat the patient with a "full-course of TB treatment
Definite case of TB
A patient is categorized as a "definite case of TB", if the diagnosis of TB is based on: (i) one or more initial sputum smear examinations positive for AFB (applicable in resource-limited settings with a functional external quality assurance system with blind rechecking); or (ii) isolation of M. tuberculosis complex from a clinical specimen, either by culture or by a newer method such as molecular line probe assay (iii) cytopathological or histopathological evidence of TB in case of extrapulmonary TB
Pulmonary TB
Active TB disease involving the lung parenchyma
Smear-positive pulmonary case of TB
A patient with one or more initial sputum smear examinations test positive for AFB on direct smear microscopy; or one sputum examination tests positive for AFB plus radiographic abnormalities consistent with active pulmonary TB as determined by a clinician.
Smear-negative pulmonary case of TB
A patient with pulmonary TB in whom: sputum smear examination was negative for AFB on atleast two occasions; radiographic abnormalities are consistent with active pulmonary TB; there is no response to a course of broad-spectrum antibiotics (except in a patient for whom there is laboratory confirmation or strong clinical evidence of HIV infection); and a decision by a clinician to treat with a full course of anti-TB treatment. A patient with positive mycobacterial culture but negative AFB sputum smears is also a smearnegative case of pulmonary TB.
New case of TB
A patient who has never had treatment for TB or who has taken anti-TB drugs for less than one month Retreatment case of TB Retreatment case of TB includes: (i) a patient previously treated for TB who is started on a retreatment regimen after previous treatment has failed (treatment after failure); (ii) a patient previously treated for TB who returns to treatment having previously defaulted; and (iii) a patient who was previously declared cured or treatment completed and is diagnosed with bacteriologically-positive (sputum smear or culture) TB (relapse).
Extrapulmonary TB
Active TB disease involving one or more extrapulmonary focus without pulmonary parenchymal involvement*

Disseminated TB
Active TB disease characterized by concurrent involvement of at least two non-contiguous organ sites; or demonstration of M. tuberculosis in the blood, or, bone marrow
Miliary TB
Miliary is a form of disseminated TB that results from a massive haematogenous dissemination of tubercle bacilli which results in tiny discrete foci usually the size of millet seeds (1 to 2 mm) more or less uniformly distributed in the lungs and the other viscera.
HIV-TB
A HIV seropositive individual is co-infected with active TB disease
* intrathoracic mediastinal and/or hilar lymph node TB or TB pleural effusion, without radiographic abnormalities in the lungs is categorized as extrapulmonary TB. If a patient with extrapulmonary TB also has involvement of lung parenchyma, the patient gets categorized as pulmonary TB (e.g., miliary TB) as per case definitions used in National Programmes for TB Control29,30; or, can be categorized clinically to have disseminated TB TB, tuberculosis; AFB, acid-fast bacilli, HIV, human immunodeficiency virus Source: Refs 34-45

Table 2: Drug Resistant Tb: Key Definitions

Resistance among new cases
Resistance to anti-TB drugs observed in isolates from new patients with TB
Resistance among previously treated cases Resistance to anti-TB drugs observed in isolates from previously treated patients with TB
Susceptible strains
Strains that respond to first-line anti-TB drugs in a uniform manner are termed “susceptible strains”
Resistant strains
Resistant strains differ from the sensitive strains in their capacity to grow in the presence of a higher concentration of anti-TB drugs
DR-TB 9,10
Isolates of M. tuberculosis resistant to any one anti-TB drug (SDR-TB); or two or more anti-TB drugs; but not amounting to MDR-TB (see below)
MDR-TB suspect11
A patient suspected of drug-resistant tuberculosis, based on RNTCP criteria for submission of specimens for drug-susceptibility testing
MDR-TB11
Isolates of M. tuberculosis resistant to rifampicin and isoniazid with or without resistance to other anti-TB drugs
Pre-XDR-TB
Isolates of Mycobacterium tuberculosis resistant to isoniazid and rifampicin (i.e., MDR-TB tuberculosis) plus (i) either any fluoroquinolone or an injectable agent, but not both20
(ii) either any fluoroquinolone or at least one second-line anti-TB drug, but not to both21
XDR-TB12
Isolates of *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin (i.e., MDR-TB tuberculosis) plus any fluoroquinolone and at least 1 of 3 injectable second-line anti-TB drugs, namely, capreomycin, kanamycin, or amikacin
XXDR-TB*13,14 Isolates of M. tuberculosis resistant to all first-line and second-line anti-TB drugs available (fluoroquinolones, ethionamide, amikacin, para-aminosalycilic acid, capreomycin, kanamycin, cycloserine) and to additional drugs (rifabutin, clofazimine, dapsone, claritromycin, thiacetazone)
TDR-TB (also called super XDR-TB)*15,16 Isolates of *M.tuberculosis* resistant to all first- and second-line licensed anti-TB drugs
*A WHO Consultation held in March 201236 suggested that “a new definition of resistance

beyond XDR-TB is not recommended, given technical difficulties with DST of many anti-TB medicines, the lack of standardized DST methods for several anti-TB drugs (including new investigational drugs) and insufficient evidence to link such DST results to treatment outcomes of patients." While the clinical and operational value of the definitions of MDR-TB and XDR-TB have been fairly evident, standardization of technical requirements for the application of terms, such as, XXDR-TB13,14, super XDR-TB15, and TDR-TB15,16, their usefulness and limitations need further clarification34-36 and these terms need to be interpreted in the proper perspective. TB, tuberculosis; SDR-TB, single drug-resistant tuberculosis; DR-TB, drug-resistant tuberculosis; MDR-TB, multi-drug-resistant tuberculosis; RNTCP, Revised National Tuberculosis Control Programme; HIV, human immunodeficiency virus; XDR-TB, extensively drug resistant tuberculosis; XXDR-TB, extremely drug-resistant tuberculosis; TDR-TB, totally drug-resistant tuberculosis.
Source: Refs. [18,19,32- 35]

TERMINOLOGY OF DRUG RESISTANCE

Primary resistance is that which has not resulted from the treatment of the patient with the drug concerned. It includes resistance in wild strains which have never come into contact with the drug (natural resistance) and the resistance occurring as a result of exposure of the strain to the drug but in another patient. Initial resistance is the resistance in patients who give a history of never having received chemotherapy in the past. It includes primary resistance and resistance to previous treatment concealed by the patient or of which the patient was unaware [36,37].

The term "acquired resistance" has often been used with the implication that resistance has developed due to exposure of the strain to antituberculosis drugs and the consequent selecting out of resistant mutant bacilli. However, some of the drug-resistant isolates in previously treated patients may actually represent primary resistance among patients who remain uncured [38,39] In the strict sense, the term "acquired resistance" can be used to refer to strains proven to have drug resistance in a reliable laboratory which were subsequently isolated from a patient in whom initial susceptibility testing was done to document the presence of a drug susceptible strain earlier [38,39]. If initial drug susceptibility testing has not been done, the term "resistance among previously treated patients" would be a more appropriate term than "acquired drug resistance" [38,39]. Susceptible strains are those that have not been exposed to the main antituberculosis drugs and respond to these drugs in a uniform manner. Resistant strains differ from the sensitive strains in their capacity to grow in the presence of higher concentration of a drug. Wild strains are those that have never been exposed to antituberculosis drugs. Naturally resistant strains are wild strains resistant to a drug without having been in contact with it. It is species specific and has been used as a taxonomic marker [36,37].

Primary drug resistance (3)

Though primary resistance is found to be low in developed countries, it is common in India and varies widely from area to area. The data on primary drug resistance estimated by different investigators over the past thirty years.

In the 1960s ICMR conducted two nationwide surveys at nine urban chest clinics in India [40,41]. The results of the first survey showed a resistance level of 8.2% to isoniazid alone, 5.8% to streptomycin alone and 6.5% to both the drugs. The primary resistance levels seen respectively in these two surveys were 14.7% and 15.5% to isoniazid and 12.5% and 13.8% to streptomycin.

A decade later, a study was conducted to assess the prevalence of primary drug resistance in Government Chest Institute and Chest (Tuberculosis) Clinic of Government Stanley Hospital, Madras [42]. The result of the study was almost similar to the earlier ICMR surveys and the authors stated that the prevalence of primary drug resistance had not risen during the span often years.

During the 80s, among five reports on primary drug resistance, though the levels of primary drug resistance to isoniazid and streptomycin were similar to the earlier

studies, rifampicin resistance started appearing in North Arcot, Pondicherry, Bangalore, and Jaipur but not in Gujarat [43-47]. The reason for the emergence of rifampicin resistance during this period may be the introduction of short course chemotherapy (SCC) regimens containing rifampicin.

Further, a higher level of primary drug resistance to isoniazid was observed in the rural population in Kolar compared to the urban patients, contradicting a Korean study where a much higher level of initial resistance was seen among urban patients giving the reason of easy access to the anti-tuberculosis drugs [48]. There was also an increase in the proportion of primary drug resistance to rifampicin (4.4%) encountered in this rural population.

In the early 1990s, a retrospective study done at New Delhi [49] showed a high level of primary drug resistance to isoniazid (18.5%) and a low level of rifampicin resistance.

Overall, the prevalence rate of primary drug resistance to isoniazid as single agent ranges from 6.0-13.0% except among the rural population in Kolar, Karnataka with a high rate of 26.7%, to streptomycin as single agent from 1.0-5.8% and to rifampicin from 0-1.9%. It is also seen from these studies that ethambutol susceptibility was not performed in many of the surveys.

For a correct evalution of primary drug resistance, standardised methodology should have been used taking care of the following namely, eliding patient history, adequate sample size, uniform laboratory methods, external and internal quality control, reliable drugs for setting up drug susceptibility, media, standard chemicals in the preparation of media etc. The outcome of Indian reports may have limitations on the above points.

TRC studies on prevalence of primary drug resistance

Data from Tuberculosis Research Centre (TRC), Chennai on primary drug resistance are available over the past 4 decades Data from 16 different chemotherapy studies from 1956 to 1995 show that there was a gradual increase in the prevalence of primary drug resistance to anti-tuberculosis drugs.

For isoniazid and streptomycin, the resistance rates were similar and ranged from 3- 13% with the highest level of 14% during 1990s for isoniazid. Initial resistance to rifampicin started appearing in 1990s and was 1.2%. Double drug resistance (SH) was also noted to a lessser extent and ranged from 0-7%. Resistance to SHR was observed to be less than 1% in 1990-95.

Acquired resistance

The rates of acquired resistance are invariably higher than the rates of primary resistance, though data on acquired resistance is limited. The longitudinal trend of drug resistance noted by Trivedi and Desai between 1980 and 1986 in Gujarat showed that in treatment failure or relapsed patients, resistance to rifampicin increased from 2.8% in 1980 to 37.3% in 1986 and to isoniazid from 34.5% to 55.8%. From this study it was presumed that high level of rifampicin resistance was almost entirely acquired [43]. When a study was conducted by ICMR in North Arcol district to compare the efficacy of SCC with the conventional (non-SCC) chemotherapy, the populations were examined during their follow-up period to confirm the bacterial quiesence and in turn the efficacy of SCC, it was found that there was an increase in the frequency of acquired drug resistance with 67% resistance to isoniazid, 26% to streptomycin and 12% to rifampicin. In addition, 6% of the strains tested were resistant to both isoniazid and rifampicin [50], A New Delhi study in the 90s also shows a higher level of acquired resistance to isoniazid and rifampicin which is almost similarto that of the Gujarat report [49].

The overall rates of acquired resistance to isoniazid ranged from 34.5-67%, for streptomycin from 26.0-26.9% and for rifampicin from 2.8- 37.3%.

Initial drug resistance

The results of the studies on initial drug resistant tuberculosis. The second ICMR survey conducted in (he 1960s showed a higher level of drug resistance among those with a history of previous chemotherapy and it was 7.0% to streptomycin and 15.8% to both the drugs" During the 80s, two surveys were conducted by 1CMR at Raichur district. Karnataka- and North Arcot district, Tamil Nadu to estimate the

prevalence of tuberculosis and the results of the survey showed a higher level of initial drug resistance in Raichur District compared to that in North Arcot District to isoniazid, 9.1%.

Data on the prevalence of drug resistance from Army Hospital, Pune showed a very low level of initial resistance to isoniazid and the authors have reasoned that this lower level of drug resistance in this population could be due to the minimal chance of indiscriminate exposure of anti-tuberculosis agents prior to reporting to the hospital [50].

Overall, the initial resistance to isoniazid as single agent ranges from 0.6-13.2%, to streptomycin from 2 2-7.0% and to rifampicin from 0-1.7%

It is also seen from these studies that ethambutol susceptibility was not performed in many of the surveys. For a correct evalution of primary drug resistance, standardised methodology should have been used taking care of the following namely, eliding patient history, adequate sample size, uniform laboratory methods, external and internal quality control, reliable drugs for setting up drug susceptibility, media, standard chemicals in the preparation of media etc. The outcome of Indian reports may have limitations on the above points.

Multi-drug resistance (MDR-TB)

The rate of MDR-TB in India is very low and ranged from 0-6%. Primary MDR-TB is found to be ≤ 3.2% arid even the level of acquired MDR-TB is ≤ 6.0% except in Gujarat where a high level was observed (11.4-18.5%)n. When compared to the prevalence of MDR-TB in other parts of the wold where upto 48% have been encountered, lower level has been reported in Indian studies

RISK FACTORS OF DRUG RESISTANCE

Three most important risk factors, identified in the causation of drug resistant tuberculosis areinappropriate previous treatment with anti-tubercular drugs, high prevalence of drug resistant tuberculosis in the community and contact with patients known to have drug resistant tuberculosis. However standardized short course chemotherapy carries a little risk of emergence of MDR-TB. Other factors that may be responsible for increased risk of resistant tuberculosis are: Co-infection with HIV, socioeconomically deprived groups in slums, prisons, correctional facilities, day care centres, intravenous drug abusers and other immuno-compromised states as in transplant recipients, anti-cancer chemotherapy recipients and patients with diabetes mellitus.

SOURCES AND CAUSES OF DRUG RESISTANCE

Multi Drug Resistant Tuberculosis is a man made problem. Blame for this goes to the government, the pharmaceutical industry, doctors, patients and their families, each of whom contributes in his/her own way to this problem. The government plays its share by providing poor infrastructure in the National Tuberculosis Control Programme, unnecessary administrative control on purchase with no proper mechanism on quality control and bioavailability tests. The pharmaceutical industry contributes by manufacturing drugs of uncertain bio-availability in fixed dose or inappropriate drug combinations, poor storage condition of drugs and substitution by inferior quality drugs by pharmacies. The doctor, by his lack of knowledge regarding doses, duration of treatment, side effects and standard regimens, frequent change of brand names and poor patient motivation, contributes the lion's share to the problem. In one of the studies where prescriptions of 449 doctors were analyzed, 75% of the doctors were found to have made some prescription error [51]. Added to this is the poor teaching and training facilities for them. Non-compliant patients due to monetary lack, lack of information, side-effects of drugs and social myths and misconceptions often do not adhere to treatment. Co-morbid conditions like diabetes, HIV, psychiatric conditions, the habits of smoking and alcoholism make the patient more vulnerable. To sum up, drug resistant tuberculosis usually results from inadequate drug therapy in multi-bacillary cases of tuberculosis, addition of single drug in cases of failure, difficulty in obtaining drugs by the poor due to lack of financial resources or social insurances, frequent shortage of second line anti-tuberculous

drugs by poor management and/or financial constrains, use of drugs or combination of drugs (FDC) with unproven bioavailability, lack of motivation at the beginning of treatment and inadequate self-administration of drugs without direct observation in the intensive phase of therapy.

Factors contributing to the emergence of drug resistance

There are several explanations given for the emergence of drug resistance.

* Deficient or deteriorating tuberculosis control programmes resulting in inadequate administration of effective chemotherapy, poor case holding, poor quality of drugs and inadequate drug supply.
* Inadequate training of health care workers regarding epidemiology, treatment and control of tuberculosis.
* Improper prescription of treatment regimens

Table 3: Global Anti-Tuberculosis Drug Resistance Situation [52]

Drugs	Drug Resistance		
	Primary (%)	Acquired (%)	Primary And Secondary
Isoniazid	0-16.9	0-53.7	-
Streptomycin	0.1-23.5	0-19.4	-
Rifampicin	0-30	0-14.5	-
Ethambutol	0-4.2	0-13.7	-
MDR	0-10.8	0-48.0	0.5-14.3

* Non-adherence of patient to prescribed drug therapy
* Increase in the number of tuberculosis patients with easy access to anti-tuberculosis medication
* The epidemic of HIV infection
* Laboratory delays in identification and susceptibility testing of M tuberculosis isolates etc.,[53,54]Drug resistant tuberculosis is mainly an iatrogenic disease arising under the selective pressure of inadequate therapy [54].

BIOLOGIC AND MOLECULAR BASIS OF DRUG RESISTANCE

Spontaneous chromosomally borne mutations occurring in M. tuberculosis at a predictable rate is thought to confer resistance to antituberculosis drugs [55-59]. A characteristic feature of these mutations is that they are unlinked. Thus, resistance to a drug is usually not associated with resistance to an unrelated drug. A tuberculosis cavity usually contains 107 to 109 bacilli. If mutations causing resistance to isoniazid occur in about 1 in 106 replications of bacteria, and the mutations causing resistance to rifampicin occur in about 1 in108 replications, the probability of spontaneous mutations causing resistance to both isoniazid and rifampicin would be 106 x 108 = 1 in 1014. Given that this number of bacilli cannot be found even in patients with extensive cavitatory pulmonary tuberculosis, the chance of spontaneous dual resistance to rifampicin and isoniazid developing is practically remote [55-59]. Thus, the fact that mutations are unlinked forms the scientific basis of antituberculosis chemotherapy. The primary mechanism of multiple drug resistance in tuberculosis is due to perturbations in the individual drug target genes [57,59]. (**Table 4**) lists the molecular mechanisms of drug resistance as they are understood today [55-59].

Scanty information is available regarding the molecular basis of drug resistance in India. In studies published from India [60,61], in addition to the previously reported mutations, several novel mutations were also observed in the rpoB (rifampicin), katG and the ribosomal binding site of inhA (isoniazid), gyrA and gyrB (ofloxacin), and rpsL and rrs (streptomycin). Mani et al [62] analysed the mutations in 44 drug resistant and six drug-sensitive M. tuberculosis clinical isolates from various parts of India in the 81-bp rifampicin resistance-determining region (RRDR) of the rpoB gene by DNA

sequencing. Fifty three mutations of 18 different kinds, 17 point mutations and one deletion, were observed in 43 of 44 resistant isolates. Three novel mutations and three new alleles within the RRDR, along with two novel mutations outside the RRDR, were reported by these workers [62]. These observations suggest that while certain mutations are widely present, pointing to the magnitude of the polymorphisms at these loci, others are not common, suggesting diversity in the multidrug-resistant M. tuberculosis strains prevalent in this region. Further, it was observed that rifampicin resistance was found to be an important marker for checking multi-drug resistance in clinical isolates of *M. tuberculosis* [37].

Table 4: Antituberculosis Drugs and the Genes involved in their Resistance

S.NO	Drug	Gene(s) involved in drug resistance
1.	Isoniazid	Enoyl acp reductase (inhA) Catalase-peroxidase (katG) Alkyl hydroperoxide reductase (ahpC) Oxidative stress regulator (oxyR)
2.	Rifampicin	RNA polymerase subunit B (rpoB)
3.	Pyrazinamide	Pyrazinamidase (pncA)
4.	Streptomycin	Ribosomal protein subunit 12 (rpsL) 16s ribosomal RNA (rrs) Aminoglycoside phosphotransferase gene (strA)
5.	Ethambutol	Arabinosyl transferase (emb A, B and C)
6.	Fluoroquinolones	DNA gyrase (gyr A and B)

Global burden of TB

The global burden of TB as described in the 16th global report on TB published by WHO in 2012 [35] most of the cases occurred in Asia (59%) and Africa (26%).

India:

Reliable data on the epidemiology of MDR-TB are lacking from India [70]. Though the problem of drug resistance was observed in the early studies from India resistance to both isoniazid and rifampicin has been a recent phenomenon. It is felt that the phenomenon of MDR-TB is on the rise and is bound to reach much more menacing proportions [66-83].

In India, prevalence of primary MDR-TB in newly diagnosed cases has been observed to be 3.4% or less (**Table 5**). Data meticulously collected at the Tuberculosis Research Centre (TRC), Chennai over the last three decades suggest that rifampicin resistance started appearing in the early 1990s and MDR-TB levels in newly diagnosed patients has been 1% or less [75].

Prevalence of MDR-TB among previously treated patients has been observed to be higher. In a study conducted at a referral tuberculosis hospital in Amargadh, Gujarat [67], multidrug resistance in previously treated cases was observed to increase from 25.2 per cent in 1983 (n=305) to 33.8 per cent in 1986 (n=260). In the North Arcot district, between 1988-89, six per cent of the 3357 patients initiated on antituberculosis treatment were found to have MDR-TB [68]. More recently, in a study from Gujarat [83], the patterns of drug resistance were studied among previously treated tuberculosis patients who remained symptomatic or smear-positive despite receiving antituberculosis drugs under the DOTS programme for a minimum period of five months. Of the 1472 patients studied, 804 (54.6%) were treatment failure cases and 668 (45.4%) were relapse cases; 822 patients (373 failure and 449 relapse) were culture positive. Of these 822 patients, 482 (58.6%, 261 failure and 221 relapse) were resistant to one or more drugs. Resistance to rifampicin and isoniazid with or without resistance to other drugs was seen in 289 of the 822 patients (35.2%). However, caution has to be exercised in interpreting the prevalence figures published in studies with a small sample size because of inherent methodological concerns.

Table 5: Prevalence of Multidrug Resistant M. Tuberculosis Isolates among New Cases in India

Place	Study period	No. of isolates tested	Resistance to isoniazid and rifampicin with or without resistance to other drugs (%)
Gujarat [67]	1983-86	570	0
North Arcot district [68]	1985-89	2779	1.6
Pondhicherry region [68]	1985-91	2127	0.7
Bangalore [69]	1980s	436	1.1
Bangalore [70]	1925-86	588	1.4
Kolar [70]	1987-89	292	3.4
Jaipur [72]	1988-91	1009	0.8
Tamil Naidu state [74]	1997	384	3.4
Composite North Arcot District [82]	1999	282	2.8
Composite Raichur District [82]	1999	278	2.5

*North Arcot district in Tamil Nadu state has now been split into two smaller districts. Composite North Arcot district refers to these two smaller districts Vellore and Tiruvannamalai

*Raichur district in Karnataka has now been split into two smaller districts. Composite Raichur district refers to these two smaller districts Raichur and Koppal Superscript numerals indicate reference nos.

CONTROL OF MULTI DRUG RESISTANT TUBERCULOSIS

The primary aim in the control of drug resistant and multi-drug resistant tuberculosis is to prevent its development in the first place. This can be done by Directly Observed Treatment Short Course (DOTS), which is the most cost effective way of treatment and prevention of MDR-tuberculosis. At the same time, since MDR-TB cases respond poorly to short course chemotherapy, careful introduction of reserve drugs to treat MDR cases to reduce further transmission of such strains will be required [84]. Since new drugs for tuberculosis are unlikely to come up in the near future, the key to success remains in prompt and correct diagnosis and effective treatment of infectious patients. Apart from a strong tuberculosis control programme, there is also a need for a continuous and periodic survey of drug resistance, which will provide information on the type of chemotherapy to be used for the treatment of patients and also serve as a useful parameter in evaluation of current and past chemotherapy programmes. There is a need for revision of guidelines of national programmes based on levels of resistance, training of professionals in private sector, strengthening of existing National Tuberculosis Control Programme, restricting use of Rifampicin (supervised and for TB and Leprosy only), taking logistic measures to ensure regular supply of drugs at all levels of National Tuberculosis Control Programme and by ensuring compliance enhancing measures like providing free/subsidized anti-tubercular drugs, supervised treatment and health education. To control the emergence of drug resistant and multi drug resistant tuberculosis, WHO in 1998 has proposed the work plan known as 'Dots Plus' for which WHO has established Green light committee [85]. The primary aims of the committee are to approve, conduct and oversee pilot projects based on guidelines for establishing 'Dots Plus' pilot projects. 'Dots Plus' is comprehensive management strategy to control tuberculosis and multi-drug resistant tuberculosis.

Because infection with drug resistant *M. Tuberculosis* is especially hazardous, special precautions should be taken to minimize the risk in contacts of these patients. Prevention has two aspects – mechanical and chemoprophylaxis. The mechanical aspects of prevention103 include proper ventilation, UV germicidal irradiation, use of masks, respirators and filtration devices and rigorous isolation of patients. The chemprophylaxis includes treatment of contacts with either Pyrazinamide (Z) and Ofloxacin / Ciprofloxacin or E and Z or Ofloxacin / Ciprofloxacin.

DIAGNOSIS OF MULTI-DRUG RESISTANT TUBERCULOSIS

It is needless to emphasize that early diagnosis and treatment of drug resistant tuberculosis is of paramount importance not only from the patient's perspective but also for the community at large. The suspicion of MDR-TB occurs in following situations:

1. History of contact with known cases of Drug Resistant/MDR-TB patients.
2. History of many courses of irregular/regular treatment of tuberculosis.
3. Clinical deterioration is the least reliable evidence of treatment failure. If there is no accompanying bacteriological or radiological deterioration, clinical deterioration is unlikely to be due to tuberculosis.
4. Radiological deterioration in chest radiograph may be a sign of treatment failure. Increase in size of cavities, increase in existing lesion and appearance of new lesion are usually signs of disease progression. One should also realize that deterioration in chest radiograph, may be due to intercurrent pneumonia, pulmonary embolism or supervening carcinoma. Therefore, radiological evidences are less reliable. However, radiological worsening in addition to positive sputum and / or clinical worsening can indicate resistant tuberculosis.
5. Persistent positive sputum smear for AFB even after 4/5 month WHO retreatment regimens.
6. Fall and rise phenomenon in which sputum smear initially becomes negative (or even less positive), and then later becomes persistently positive. This indicates failure usually due to either the patients having ceased to take the drugs or to the development of resistance to all the drugs patient is receiving.
7. Report of sensitivity results indicating resistance to at least Isoniazid and Rifampicin is gold standard for the diagnosis of MDR-TB. However, one has to keep in mind the limitation of highly specific test because the technique is complex and difficult to perform accurately even when skilled personnel are available and laboratory facilities are of a high standard. Further one should also realize that laboratories vary in reliability, error occurs in labs, different sensitivity reports are obtained of the same patient from different laboratories. There is a lack of standardization, coordination and crosschecking with national and supranational reference laboratories in our country. Keeping above background in mind, it is pertinent that sensitivity test result should not be accepted uncritically, they should always be correlated with history, smear results and x-ray and should be used as a guide for future therapy and should not dictate treatment options. Therefore there is urgent need to develop standard laboratories under quality control of national and supranational reference laboratories in our country.
8. Newer molecular techniques like DNA sequencing, Line Probe Assay (LiPA), DNA microarrays, molecular beacons, Single strand confirmation polymorphism, fluorescent Resonance Energy Transfer probes, other PCR based techniques and Mycobacteriophages based assays like FAST Plaque TB and Luciferase receptors phages (LRPs) have been used for identification of resistance associated mutation. The expectation that molecular techniques would surpass conventional methods has yet not been realized because most of techniques still require detailed and systemic evaluation using standard techniques.

LABORATORY DIAGNOSIS OF MDR-TB AND XDR-TB

Drug-resistant TB often goes undetected and untreated in many countries. With the exception of a few developed countries, most national TB programs worldwide do not routinely provide diagnostic services based on culture and DST. The laboratory is an essential component in TB control programs, and broader access to DST is a priority for most countries. Early choice of appropriate treatment is an essential determinant of favourable outcome, and rapid determination of drug resistance can allow a customized approach to treatment early in the course of the disease and can potentially reduce morbidity, mortality and infectiousness [88].

The diagnosis of MDR-TB and XDR-TB is hampered by the absence of effective and affordable rapid diagnostic techniques for drug sensitivity. Several approaches, phenotypic and molecular, have been explored to develop rapid, reliable and accurate methods for the rapid detection of drug resistance in M tuberculosis. These methods should also be evaluated and applied in high-incidence areas.

CONVENTIONAL CULTURE-BASED METHODS

Using standardized DST procedures with conventional methods, eight to 12 weeks are required to identify drug resistant microorganisms on solid media (i.e., Lowenstein-Jensen medium). In general, such methods assess inhibition of M tuberculosis growth in the presence of antibiotics to distinguish between susceptible and resistant strains.

The proportion method allows precise determination of the proportion of resistant mutants to a certain drug; the resistance ratio method compares the resistance of an unknown strain with that of a standard laboratory strain. While relatively inexpensive and undemanding of sophisticated equipment, results usually take weeks and this is challenging; inappropriate choice of treatment regimen may result in death within weeks of initiation, such as in the case of XDR-TB (especially in HIV-infected patients). In addition, delayed identification of drug resistance results in inadequate treatment, which may generate additional drug resistance and continued transmission in the community.

LIQUID CULTURE-BASED METHODS

Automated liquid culture systems are more sensitive than solid media cultures, and they significantly reduce turnaround time. However, even with liquid cultures, two to four weeks are still needed to obtain results, and their substantially higher cost is an issue for resource-limited countries. The BACTEC 460 TB radiometric system (Becton Dickinson, USA) was considered to be a major advancement when it was introduced, but has been replaced by the Mycobacteria Growth Indicator Tube system (Becton Dickinson, USA). Several published studies have shown the excellent performance of the Mycobacteria Growth Indicator Tube system for the rapid detection of resistance to first- and second-line anti-TB drugs [89]. Detection of drug resistance can be accomplished in days rather than weeks, although still constrained by high cost (equipment and consumables).

In 2007, the WHO issued policy guidance on the use of liquid TB culture, DST and rapid species identification in low-resource settings [90]. The WHO policy recommends phased implementation of these systems as a part of a country-specific comprehensive plan for laboratory capacity strengthening, and addresses key issues including biosafety, customer support, staff training, maintenance of infrastructure and equipment, specimen transport and reporting of results.

NOVEL, RAPID PHENOTYPIC METHODS

Among novel, rapid phenotypic methods, the microcolony method is relatively low cost. It has been adapted for the rapid detection of drug resistance directly from sputum samples, and has been shown in early studies to be accurate for the detection of MDR-TB compared with the reference proportion method, with results available in one week [91]. Newly developed phenotypic tests such as TK Medium (Salubris Inc, USA), microscopic-observation drug-susceptibility assay (MODS) and FAST Plaque-Response bateriophage assay (Biotec Laboratories Ltd, UK) are usually cheaper but not always

simple to perform, with some requiring high standards of biosafety and quality control [92].

TK Medium is a novel colorimetric system that indicates growth of mycobacteria by changing the colour of the growth medium. Metabolic activity of growing mycobacteria changes the colour of the culture medium, and this allows for an early positive identification before bacterial colonies appear. TK Medium also permits susceptibility testing for drug resistance, and can allow for differentiation between M tuberculosis and non tuberculous mycobacteria. Unfortunately, there is insufficient published evidence on the field performance of this test in developing countries [92].

The MODS assay is based on the observation of the characteristic cord formation of M tuberculosis that is visualized microscopically in liquid medium with the use of an inverted microscope [93]. MODS uses simple light microscopy to detect early growth of M tuberculosis as 'strings and tangles' of bacterial cells in the broth medium with or without antimicrobial drugs (for DST) [94]. The agreement between MODS and the reference standard for drug susceptibility testing is 97% for INH, 100% for RIF, and 99% for INH and RIF combined (MDR). Lower values of agreement were obtained for ethambutol (95%) and streptomycin (92%). One minor disadvantage of MODS is the requirement for an inverted microscope for observation of the mycobacterial growth.

FAST Plaque-

Response is a phage amplification-based test, and has been developed for direct use on sputum specimens. Drug resistance is diagnosed when M tuberculosis is detected in samples that contain the drug (ie, RIF). A recent meta-analysis of the accuracy of phage-based methods for detecting RIF resistance in M tuberculosis concluded that these assays performed on M tuberculosis culture isolates have high sensitivity, but variable and slightly lower specificity [95]. Not enough evidence is available on the accuracy of these assays when performed directly on sputum samples. Safety and quality control issues related to the use of this technique should also be addressed carefully.

Several colorimetric methods have also been proposed in the past few years for the rapid detection of drug resistance in M tuberculosis. A recent systematic review and meta-analysis [96] of colorimetric redox indicator methods found evidence of high sensitivity and high specificity for the rapid detection of MDR-TB. Colorimetric methods represent a good alternative for the rapid detection of drug resistance in laboratories with limited resources. However, these tests cannot be directly used on clinical specimens.

Overall, large multicentric studies defining the accuracy of phenotypic DST methods are still unavailable. Practical issues, such as quality controls and training requirements, have not been adequately addressed under field conditions. The application of these approaches to support individualized treatment through determination of second-line drug susceptibility profiles remains largely unexplored, implying that their application in support of individualized treatment of MDR-TB (and especially for XDR-TB) remains uncertain.

NOVEL, RAPID MOLECULAR METHODS

The identification of specific mutations responsible for drug resistance has facilitated the development of novel, rapid molecular tools for DST. The detection of RIF resistance is traditionally used as a predictor of MDR-TB – its positive predictive value is a function of the sensitivity and specificity of RIF resistance testing and the prevalence of MDR and non-MDR RIF resistance, which is highest among previously treated cases in settings with high MDR prevalence and low non-MDR RIF resistance. Molecular tools are based on nucleic acid amplification in conjunction with electrophoresis, sequencing or hybridization. Although most of the techniques were initially developed to detect drug resistance in TB complex isolates, they are being evaluated for direct detection of TB complex isolates and identification of alleles related to drug resistance in clinical specimens (such as sputum). Their potential advantage is that there is no need for growth of the organism and DST results can be determined in days

rather than weeks; research suggests that they can be highly reliable.

Direct sequencing is another approach to detecting mutations, but it is an expensive and time-consuming process. Techniques, such as real-time polymerase chain reaction, that make use of wild-type primer sequences to amplify genes and enable the use of specific probes (ie, molecular beacons) to identify mutations are expensive and complicated, even if highly sensitive and specific. Reverse hybridization-based assays, referred to as line probe assays, represent a useful tool for their superior cost-effectiveness. These tests are based on the hybridization of specific probes for wild-type and mutated sequences of genes involved in drug resistance, and they show high specificity and medium/high sensitivity.

Commercially available line probe assays include the INNO-LiPA Rif. TB kit (Innogenetics, Belgium) and the GenoType MTBDR assay (Hain Lifescience, Germany). A recent meta-analysis summarized the results obtained for the INNO-LiPA Rif. TB test, and showed that this line probe assay has high sensitivity and specificity when culture isolates are used [97]. The majority of studies had sensitivities of 95% or greater, and nearly all were 100% specific. The results, however, are less accurate when the test is directly applied to clinical specimens (ie, sputum). There is a paucity of data on the application of this test directly to clinical specimens.

The Geno Type MTBDR test is able to detect mutations in the rpoB gene for RIF resistance, and the most frequent mutation at codon 315 of the katG gene for INH resistance, either in isolates or clinical specimens. The specificity and sensitivity of the assay for RIF resistance were nearly 100%; for INH-resistance, despite a high specificity (approximately 100%), the sensitivity of the test ranged from 70% to 90%, depending on the prevalence of the particular mutation at the katG locus . GenoType MTBDRplus (Hain Lifescience, Germany), an advanced version of the assay, includes probes for the identification of other mutations in the hotspot region of the rpoB gene for RIF resistance, and probes to detect mutations in the promoter region of the inhA gene involved in INH resistance. These improvements facilitate the detection of another 10% to 20% of INH-resistant cases, with an enhancement in rapid MDR-TB diagnosis.

Overall, line probe assays are accurate and useful for rapid detection of drug resistance directly in clinical specimens. However, the number of genes that can be analyzed remains limited and the test fails to distinguish insertion mutations. Furthermore, they retain a lower sensitivity among acid fast bacilli-negative samples. In general, line probe assays are expensive and require sophisticated laboratory infrastructure. Their role and utility in low-income, high-burden countries will need to be evaluated in field studies.

TREATMENT OF MULTI-DRUG RESISTANT TUBERCULOSIS

The management of multi-drug resistant tuberculosis is an area that has been shrouded in a lot of myths and misconceptions, and therefore utterly chaotic. Though treatment guidelines, including standardized, empirical and individualized approaches have been laid down by the WHO, but therapy should be tailored to the needs of the particular patient.

Basic principles of chemotherapy in multi-drug resistant tuberculosis [98 – 102]

1. Treatment should be in a specialized centre with standard laboratory facilities.
2. Early diagnosis of MDR-TB and prompt initiation of treatment are important for successful outcome.
3. Designing an appropriate regimen needs experience and skill. Regimen should be based on previous history of anti-tuberculous drugs taken by the patients. Drugs susceptibility test when available from reliable laboratories should be used to guide therapy.
4. Regimens should contain at least four drugs that are highly likely to be susceptible based on drug susceptibility test and/or previous intake of antituberculous drugs by the patient. Often more than four drugs may be started if the susceptibility pattern is unknown, if effectiveness is questionable for an agent(s) or if extensive, bilateral pulmonary tuberculosis is present.

5. Use any first line oral agent to which isolate is sensitive. Use one injectable, one fluoroquinolone and add as many second line bacteriostatic agentsas needed to complete the regimens. Injectable agent should be continued for atleast six months.
6. Never add a single drug to a failing regimen.
7. It is ineffective to combine two drugs of the same group or to combine in the prescribed chemotherapy regimen a drug potentially ineffective because of cross-resistance. Cross resistance has been reported between Thioamides and Thioacetazone, Kanamycin/ Amikacin with Streptomycin, Rifampicin with Rifapentine, Rifabutin (>70% strains) and among various derivatives of fluoroquinolones. Cross-resistance has also been reported between Ethionamide and Isoniazid, Viomycin and Kanamycin, Viomycin and Capreomycin. Strains resistant to Streptomycin/Kanamycin/Amikacin are still sensitive to Capreomycin.
8. All the drugs should be given in a single daily dose preferably, except PAS which is usually given in two divided doses in order to avoid problems of intolerance. Among Thioamides, Prothionamide is better tolerated than Ethionamide.
9. Intermittent therapy is usually not effective and should be avoided in multi-drug resistant tuberculosis.
10. No drug should be kept in reserve and the most powerful drugs (bactericidal) should be used initially and in maximum combination so as to ensure that the first battle is won and won permanently.
11. Therapy should be under direct observation preferably for 3-4 months or till the sputum conversion.
12. Surgical treatment should be considered as an adjunct to chemotherapy wherever applicable, as results of chemotherapy are very unpredictable.
13. All measures should be taken to persuade and encourage patients not to stop treatment despite all its discomforts, as it is the last that stands between patient and death.

MDR TB TREATMENT

New delhi [103]:

Ahead of world tuberculosis day on March 24 2016, government today launched Bedaquiline, a new class of antituberculosis medicine discovered to specifically treat drug resistant TB in India.

The drug which has been approved by Drug Controller General of India [DCGI] for the treatment of pulmonary multi-drug resistant TB [MDR-TB] in combination with an optimized background regimen was launched.

"The new anti-TB drug & is indicated for use in the treatment of drug-resistant TB Bedaquiline is being introduced at six identified tertiary care centres across India. Bedaquiline will be given to multi-drug resistant TB patient with resistance to either all fluoroquinolone and or all second line injectables and extensive drug resistant TB.

Table 6: Medicines Recommended for the Treatment of Rifampicin-Resistant and Multidrug-Resistant TB [104]

A. Fluoroquinolones2	Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second-line injectable agents	Amikacin Capreomycin Kanamycin (Streptomycin)3	Am Cm Km (S)
C. Other core second-line agents2	Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents	Pyrazinamide	Z

(not part of the core MDR-TB regimen)	D1	Ethambutol High-dose isoniazid	E H^h
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	p-aminosalicylic acid Imipenem-cilastatin4 Meropenem4 Amoxicillin-clavulanate4 (Thioacetazone)5	PAS Ipm Mpm Amx-Clv (T)

CONCLUSION

Effective control of MDR-TB and XDR-TB will require massive scaling-up of culture and DST capacity, and the expanded use of novel and rapid assays for drug resistance. Several pilot projects are underway in resource limited countries that will provide necessary evidence to design policy guidelines for management of MDRTB. It must also be emphasized that even optimal treatment of multi-drug resistant tuberculosis will not alone curb the epidemic; efforts must be focused on the effective use of first line drugs in every category I and category II patients as practised in Revised National Tuberculosis Control Programme so as to prevent the ultimate emergence of multi-drug resistant tuberculosis. Adoption of Directly Observed Treatment - short course (DOTS) to prevent multi-drug resistant strains and careful introduction of second line drugs to treat patients with MDR-TB are the top priorities for the proper control of MDR-TB. Overall, molecular approaches are still insensitive for many of the mutations that allow some TB strains to remain resistant to second-line drugs due to our limited understanding of the underlying biological mechanisms. Furthermore, all genotypic tests require DNA extraction, gene amplification and detection of mutation and are, therefore, relatively expensive and demand resources and skills that are usually unavailable in most regions where rates of MDR-TB and XDR-TB are high. The challenge, therefore, is to not only develop new tools, but to also make sure that benefits of promising new tools actually reach the populations that need it most, but can least afford them.In conclusion, treatment of MDR-TB is a challenge which should be undertaken by experienced clinicians at centres equipped with reliable laboratory service for mycobacterial culture and in vitro sensitivity testing. Judicious use of second-line drugs, supervised individualised treatment, focussed clinical, radiological and bacteriological follow-up, judicious use of surgery at the appropriate juncture are key factors in the successful management of these patients. In certain areas, currently available programme approach may not be adequate and innovative approaches such as DOTS-plus may have to be employed to effectively control MDR-TB.

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