

Multi Drug Resistant Tuberculosis

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INTRODUCTION

The development of antituberculosis treatment is characterized by increasing knowledge about principle of treatment,

was recognised in 1946 immediately following the introduction of streptomycin². A significant land mark soon followed with the discovery, that multiple drug therapy was able to cure tuberculosis without development of drug resistance³. Later on it was shown that streptomycin resistance could be largely overcome with the addition of isoniazid and paraaminosalicylic acid, and that such 3 drug regimen was able to cure tuberculosis patients who had no previous treatment in 100% of cases without creating drug resistance⁴. These warnings went unheeded and isoniazid resistance became a major problem⁵. Fortunately the introduction of rifampicin plus pyrazinamide containing treatment regimen helped to overcome and successfully treat even those patients with strains initially resistant to isoniazid⁶. The most recent chapter in complacency over well established principles has resulted in the emergence of combined Isoniazid.-rifampicin resistance.

DEFINITIONS

Drug Resistance

From a clinical stand point, drug resistance can be defined as a temporary or permanent capacity of the organisms and their progeny to remain viable or to multiply in the presence of the concentration of the drug that would normally destroy or inhibit the growth of other cells⁷.

Wild Strain

It is defined as a strain of Mycobacterium tuberculosis complex which has never been exposed to any antibacterial drug.

Natural Resistant Strains

These are wild strains resistant to a particular drug without ever having been in contact with it. Thus neither the patient with naturally resistant bacilli nor his source of infection had chemotherapy in the past. Examples of this type of resistance include *M. bovis* resistance to pyrazinamide and *M. africanum* resistance to thiacetazone. Natural resistance is a species-specific resistance which can be used as a taxonomic marker useful in species identification. Naturally resistant strain should be clearly distinguished from wild type resistant mutant. These mutants occur as a result of genetic mutations that precede contact with the drug. These spontaneous mutants are found in wild *M. tuberculosis* strain with frequencies which vary for different drugs: they are in the order of 10^6 for isoniazid and 10^8 for Rifampicin (Table 1).

Table 1

Spontaneous Occurrence of Drug-Resistant Mutants in Wild Strains of Mycobacterium

Drugs	Probability of resistance
Rifampicin	10^8
Isoniazid, Streptomycin, Ethambutol Kanamycin, PAS	10^6
Ethionamide, Capreomycin, Viomycin, Cycloserine, Thiacetazone	10^3

Primary Resistance

It is defined as the presence of drug resistance to one or more antituberculosis drugs in a tuberculosis patient who has never received prior tuberculosis chemotherapy. It is caused by infection with drug resistant organism from another patient who had acquired resistance either due to inadequate chemotherapy or because of infection with primary drug resistant organism. It is often difficult to differentiate primary from undisclosed acquired resistance.

Acquired Resistance

It is defined as resistance to one or more antituberculosis drugs which arises during the course of treatment, usually as a result of non-adherence to the recommended regimen or faulty prescribing. This can also be referred to as secondary resistance. Emergence of acquired resistance in a patient receiving chemotherapy is serious and one of the frequent reasons of treatment failure⁸.

Initial Resistance

It is defined as the presence of drug resistance to one or more antituberculosis drugs in a new tuberculosis patient who presents to a treatment centre. This category include those patients with primary resistance as well as those with undisclosed acquired resistance who either do not remember prior treatment, refuse to divulge the information on past treatment, or were not appropriately asked about treatment history. Initial resistance does not include chronic patients.

Multi Drug-Resistance

This refers to resistance to more than one antituberculosis drug. This type of resistance, which is man made, can occur both as primary and secondary resistance. Practically, multidrug resistance is defined as resistance to atleast both Isoniazid and Rifampicin⁹.

Chronic Patient

This is defined as a patient who has failed a long, often irregular, course or courses of therapy, and who is now likely to

present with acquired resistance to one or more antituberculosis drugs. Alternatively, this is defined as a patient who remains smear-positive after completing a retreatment regimen under supervision.

EVOLUTION OF MULTI DRUG RESISTANT STRAINS

Understanding how *M. tuberculosis* can acquire drug resistance is essential to prevent the emergence of drug resistant strains. Tubercle bacilli have spontaneous mutation of the bacterial chromosome that confer resistance to antimicrobial agent¹⁰. These mutation occurs at a low rate which varies depending upon the drug. For example spontaneous resistance to Isoniazid occurs in approximately 1 in 10⁶ organism and to Rifampicin in 1 in 10⁸ organism¹¹. The emergence of drug resistance represent the survival of random preexisting mutations, not a change caused by exposure to the medication¹⁰.

These mutations are unlinked; hence resistance to a drug is generally not associated with resistance to an unrelated drug. Therefore, the probability of resistance to multiple drugs is multiplicative. For example the probability of developing resistance simultaneously to Isoniazid and Rifampicin is the product of the incidences of resistance to the individual drug¹¹, that is 1 in 10¹⁴ (1 in 10⁶ x 1 in 10⁸). A tuberculosis cavity will normally harbour 10 million to 1 billion (10⁷ to 10⁹) bacilli¹². Thus, the likelihood of occurrence of a mutant resistant to two drugs is extremely low⁸. In a cavity due to susceptible organism, one may predict that there will be several hundred resistant mutant to Isoniazid and few resistant to Rifampicin; but none resistant to both drugs. Administration to both Isoniazid and Rifampicin in such situation should lead to a cure, as Isoniazid resistant organisms will be killed by Rifampicin and Rifampicin resistant organism will be killed by Isoniazid. If the individual takes only a single drug, or changes the regimen so that it contains only one drug to which the organism is susceptible (effectively equivalent to monotherapy), the risk of selecting the organism resistant to the susceptible drug is high. Therefore, by treating tuberculosis with two or more drugs in combination, mutant resistant to any single drug are killed by one or the other drugs in the regimen, and the selection of drug resistant organism can be prevented.

Inappropriate prescribing practices by clinician can also lead to the selection of drug resistant organism^{13,14}. The most common errors were addition of single drug to a failing regimen. Failure to identify preexisting or acquired drug resistance, and administration of initial regimen inadequate in number of drugs or duration or both. For example, if resistance to Isoniazid is not suspected in a patient with Isoniazid resistant disease, therapy with Isoniazid and Rifampicin

is equivalent to therapy with Rifampicin alone. In this situation all the organisms in the cavity will be resistant to Isoniazid, and a small number will spontaneously mutate and develop Rifampicin resistance as well. Administration of Isoniazid and Rifampicin in this setting is equivalent to monotherapy with Rifampicin alone. Initial clinical improvement may occur as Rifampicin will kill all the sensitive organisms. This will select few organisms resistant to both drugs, to flourish in the cavity, and eventually the disease will relapse with MDR-TB. To prevent the development of multiple drug-resistant tuberculosis Ethambutol is recommended along with Rifampicin, Isoniazid, Pyrazinamide in the initial intensive phase in areas where primary INH resistance is four or more percent¹⁵.

History of prior treatment is important for development of MDR-Tuberculosis. The risk of acquired resistance increases with the length of treatment. Even 2 weeks of monotherapy with isoniazid can produce 25 percent resistant isolates¹⁶. The risk increases to 60 percent with six month and to more than 80 percent after 2 years of monotherapy.

GLOBAL PREVALENCE OF MDR TUBERCULOSIS

No one knows the extent of drug resistant tuberculosis, nor how fast it is spreading. A global surveillance system has been put in place by WHO to try to answer these questions, but it will be year or two before a clear picture begins to emerge. Mean while the evidence from scattered literature gives good reason to be alarmed. The prevalence of acquired resistance ranges from 20 to 80 percent. The proportion of MDR cases in previously treated patients varies from 4 to 48% and represent 20 to 65 percent of patients will acquired resistance¹⁷. Initial MDR tuberculosis is probably very low. The higher the prevalence of MDR tuberculosis in previously treated patients with acquired resistance, the higher is the risk of transmission of MDR bacilli to uninfected individuals. In some countries or areas, the prevalence of MDR tuberculosis among new patients varies from 2.5 to 56.5¹⁷.

PREVALENCE OF MDR TUBERCULOSIS IN INDIA

In India there has been paucity of reports due to lack or limited access to testing drug susceptibility. Therefore, much of the drug resistance has been presumed clinically. The available literature indicates that primary/initial drug resistance is mainly to isoniazid. That too is also of varying order but less than 20 percent^{18,20}. Initial multidrug resistance is probably very low.

MDR- tuberculosis is more common in previously treated

Table 2
Prevalence of Multidrug Resistance in India

S. No.	References	Initial Drug Resistance			Acquired Drug Resistance			
		Total %	H %	R %	Total %	H %	R %	H + R %
1.	Trivedi SS et. al., 1992	20	13.9	0	55.8*	37.3**	33.6	
2.	Jain N K et. al., 1992	19	18.5	0.6	60	50.7	33.3	33.3
3.	Gupta PR et. al., 1993	19.1	10.1	3.0	-	-	-	-
4.	Paramasivan CN et. al. 1993							
	a) Pondicherry	13	6	0.9	-	-	-	-
	b) North Arcot	25	13	2	-	-	-	-
5.	Datta M, et. al., 1993	-	-	-	70	67	12	6

* There was a marked increase in isoniazid resistance from 34.5% in 1980 to 55.8% in 1986.

** Rifampicin resistance increased significantly from 2.8% in 1980 to 37.3% in 1986.

patients (Table 2). It constitutes 33-35% of patients who have failed with Rifampicin containing regimen^{18,19}. Acquired resistance to Rifampicin (33-35%) and Isoniazid (50-55%) is substantial^{18,19}. Strains resistant to Rifampicin were usually resistant to Isoniazid, where as converse was not necessarily true¹⁸. Few strains resist almost all known anti-TB drugs.

CLINICAL SIGNIFICANCE OF DRUG RESISTANCE

A six month short course chemotherapy was established as a cure of tuberculosis in 1980s after several well controlled studies²³. Today, the most widely accepted regimen is the combination of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol or Streptomycin daily for 2 months, followed by Isoniazid and Rifampicin daily for 4 additional months. This regimen is highly effective. Intermittent short course therapy with drug administration directly observed thrice a week in intensive phase and continuation phase is also equally effective²⁴⁻²⁵. The presence of drug resistant organisms at the start of therapy increases the risk of treatment failure many folds²⁶⁻²⁷. Initial resistance to single drug such as Isoniazid or Streptomycin could be treated successfully with six months of short course chemotherapy²⁶. The resistance to Rifampicin is a serious problem. The success rate is much lower among patients with organism resistant to rifampicin and isoniazid. About 70-90 percent patients with isoniazid and rifampicin resistant bacilli did not respond or relapsed to treatment with short course chemotherapy^{26,27}.

DIAGNOSIS OF MDR-TB

When a patient of tuberculosis on TB treatment fails to respond or deteriorates, one should need to consider:

Was the initial diagnosis of tuberculosis correct?

Is the patient taking drugs regularly and in adequate dosages?

Is the drug resistance a probability?

Is there some new disease that has occurred?

At times review of diagnosis of tuberculosis may be necessary if initial diagnosis was not based on positive sputum smear. Any evidence of new disease in terms of symptoms, signs or abnormalities in investigations should be considered. At this stage three specimens of sputum should be examined for AFB and fresh chest x-ray should be done. If the diagnosis is not in doubt, the patient has been fully compliant with treatment and no new disease is present, then drug resistant should be suspected. Unless the sputum is positive for AFB, one cannot diagnose multidrug resistant tuberculosis. For example, a patient may have a destroyed lung all throughout his life, unless such a patient is sputum positive one cannot consider such a patient a suspected case of drug resistance.

To confirm the resistance it is desirable to have sputum culture for *Mycobacteria* and drug susceptibility tests. Unfortunately in our country there are very few reliable laboratories where culture and sensitivity facilities are available. At such time resistance to a particular drug can be assumed on the basis of clinical criteria. For example in a patient who fails to become smear and culture negative during a regimen consisting of Rifampicin, Isoniazid and Pyrazinamide, when susceptibility testing result become available 2 months after treatment, initial resistance to isoniazid and rifampicin is found. In this setting of 2 month of monotherapy with Pyrazinamide, it is safer to assume that resistant to pyrazinamide has developed. Therefore, the diagnosis of MDR tuberculosis can be assumed on the basis of a clinical criterion: failure or relapse after 2 courses of chemotherapy, atleast one of which was directly observed¹⁷. This criterion defines the 'chronic cases' which are

likely to be due to MDR bacilli: a chronic case of tuberculosis is a case that remains smear positive after completing a retreatment regimen under supervision as defined by WHO²⁸.

MANAGEMENT OF MULTI-DRUG RESISTANT TUBERCULOSIS

Treatment of drug resistant tuberculosis is frustrating than drug susceptible tuberculosis. It is difficult to prescribe standard regimen for MDR tuberculosis cases. The treatment required to be individually tailored. Despite the lack of controlled clinical trials, there are several principles that should be followed for selecting a regimen for these patients. The drugs used in the treatment of MDR-TB are generally less effective³⁰⁻³¹. Most experienced clinicians, recommend minimum of three or four and possible as many as six or seven drugs³⁰⁻³⁴. The regimen should include atleast three drugs for which the patient's organism have proven in vitro susceptibility and preferably that have not been used to treat the patient before³¹⁻³⁵.

Decision regarding optimal drug selection for the treatment of MDR-TB are best made with the assessment of treatment history and with the aid of drug susceptibility testing. If the results of drug susceptibility will not be available for two to four months. It might be prudent to add several new drugs. Therefore, it is crucial to elicit a proper history of previous treatment. Prior therapy with a drug for more than a month must be regarded with suspicion even if no resistance was demonstrated at that time³⁴. Treatment histories are not always adequate. Therefore, meticulous study of records of therapy provide good premium.

Early drug susceptibility test results are usually not available with conventional methods, although the tests can be done far more rapidly. For example, nearly all sputum specimens that contain many organisms (smear positive) can be tested adequately with BACTEC system within two weeks. Three to five weeks are required for smear negative specimen. Such facilities are not easily available. Even then drug susceptibility test should be done. Obtaining the result of susceptibility test allow the treatment to be modified in a timely manner to protect against further acquired drug resistance and to diminish the potential toxicity of empirical five or six drug regimen. Some times problem may arise if different susceptibility patterns are found at different times in the treatment course; two different sensitivity reports are obtained from two different laboratories; the sensitivity report does not correlate with clinical findings or clinical judgement of what the patient is resistant to. In such circumstances it is appropriate to assume the worst combination of resistance that has been found and design a new regimen accordingly. In addition the experience and quality of the microbiology laboratory must be considered in accepting the result. Drug susceptibility test should not be used in isolation to clinical response to treatment. A patient with persistent positive smears and cultures despite a regimen to which in vitro susceptibility has been demonstrated merits a complete reevaluation of treatment strategy, and particularly require confirmation that the individual has actually adhered to the prescribed regimen.

MONITORING TREATMENT

Improvement in the results of bacteriologic tests of sputum is the main marker of response, but decreased fever, cough, sputum, and weight loss are important indirect indicators. Improvement on the chest x-ray may lag behind other changes. Therefore, sputum smear AFB should be examined every month.

The optimal duration of treatment of MDR-TB has not been clearly identified. Because of the high risk of relapse, treatment for multidrug resistance is usually continued for 24 months after culture has converted to negative³⁶.

Since most patients cannot tolerate therapy with an injectable drug for that length of time, injectable drugs are usually administered for 4 to 6 months if toxicity does not intervene³⁶.

Experience with large number of patients with multidrug resistant tuberculosis indicates that if chemotherapy is to achieve sputum conversion, it will do so within five months in most patients³⁰. If sputum conversion does not occur or the patient relapses, further acquired resistance to the agents being used will appear. Hence, if chemotherapy is not successful the potential benefit of surgery should be considered.

The Role of Surgery

Surgical treatment offers benefit for patients with chronically positive sputum³⁷⁻⁴⁰. Surgery is indicated in patients with poor response to medical therapy, disease sufficiently localized to permit resection of the bulk of involved lung and adequate cardiorespiratory insufficiency. Selection of surgical candidates and timing of adjunctive surgery must be performed on a patient by patient basis. The goal of surgery must be to remove as much diseased lung as possible, particularly cavities, while not causing crippling respiratory impairment. This does not preclude such procedures as bilateral upper lobectomies. The anticipated site of the surgical stump must be evaluated by bronchoscopy immediately prior to surgery to ensure the absence of endobronchial tuberculosis, which would risk bronchopleural fistula.

Drugs Used in the Treatment of MDR Tuberculosis

Second line agents are indicated for treatment of MDR-Tuberculosis, when the infecting organisms are resistant to two or three first line or primary drugs. (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, Streptomycin). Second line drugs are chemotherapeutic agents other than first line agent which have been shown to be active against *M. tuberculosis* in clinical, animal and laboratories studies. They are less potent and more toxic when compared with first line drugs. Their usefulness is often limited by toxicities and undesirable side effects. The second line agents currently in use are: Ethionamide, Cycloserine, Kanamycin, Capreomycin and PAS.

Ethionamide

It is a companion drug in the treatment of drug resistant tuberculosis. It is available as 250 mg tablets. The most common side effect of ethionamide is gastric intolerance, consisting of nausea and after ingestion an unpleasant metallic taste in the mouth and epigastric burning pain. Most of the symptoms disappear within a week, but in some patients the symptoms are severe and persistent, requiring discontinuation of therapy⁴¹.

Hepatitis and jaundice is another complication that has been reported to occur in 4-5 percent of patients. Hepatitis can occur as long as 5 months after the start of therapy. Whether this is a result of hypersensitivity or a direct effect of the drug on the liver is not known. When treatment is withdrawn, hepatitis usually resolves. Transient abnormalities of liver function have also occurred but values returned to normal even when therapy was continued⁴¹.

Other side effects include mental depression, peripheral neuritis, convulsion, gynecomastia, dizziness, photosensitivities, alopecia, menstrual disturbances, and acne. Teratogenic effect has been reported in animals; hence use in pregnancy is not advised⁴³. The adverse reactions on the central nervous system attributed to ethionamide, cycloserine and isoniazid maybe additive⁴⁴, and caution maybe exercised when using these drugs in combination.

Prothionamide

It is similar to ethionamide in its antibacterial and other effects,

but less unpleasant and is tending to replace the latter.

The usual dose of ethionamide/prothionamide is 500-1000mg daily in divided doses. The maximum optimum daily dose is 15-20 mg/kg. Some patients are unable to take this amount and it may be necessary to accept a daily dose of 750 mg or even 500 mg in patients weighing less than 50 kg. Patients may find the drug more acceptable if it is administered with milk or before retiring. If possible it should be administered once daily, alternatively twice daily with meals. If difficulties encountered the dose maybe increased gradually from 125 mg to full dose over a period of 7 to 10 days.

Cycloserine

It has a relatively weak effect against *Mycobacteria*⁴². It is used in combination with other antituberculosis drugs in the treatment of *M. tuberculosis* patient resistant to two or more first line agents. Cycloserine is given at a dose of 10mg/kg/day in divided doses upto 1 g/day. It is available as 250 mg capsules and the usual adult dose is 250mg given twice or three times a day. Cycloserine is well tolerated in terms of gastrointestinal side effects, but it has substantial potential central nervous system toxicity. Toxic reactions occurred in about 15 percent of patients; in about half the patients convulsive seizure occurred. Other reactions reported are psychotic episodes, suicidal ideation, somnolence, emotional changes, hyperactivity and personality changes. Complications appear more frequently in alcoholics, those with a history of seizure disorder or psychiatric disorder, and patients with impaired renal function. Pyridoxine in a dosage of 50 mg per 250 mg of Cycloserine, may relieve or prevent some neuro toxic effects. Sedative may control anxiety and tremors, and anticonvulsant will control convulsion. If symptoms of neurotoxicity occur, the dosage should be reduced or the drug discontinued.

Kanamycin, Amikacin and Capreomycin

Injectable medication include kanamycin, amikacin and capreomycin. Kanamycin and amikacin are aminoglycosides. Capreomycin is a polypeptide. These agents offer no advantage over streptomycin in the treatment of TB except against some drug resistant organisms and they have similar to worse toxicity profile. Toxicity and side effects include nephrotoxicity, vestibular dysfunction, hearing loss, rarely chemical imbalance (decrease in calcium, potassium, and magnesium), circumoral numbness, and minor dizziness.

Amikacin and kanamycin are not used simultaneously owing to close similarity of these aminoglycosides and the additive ototoxicity and nephrotoxicity. Occasionally capreomycin is used with amikacin or kanamycin if there is difficulty in tailoring an effective regimen. Older patients experience less renal and eighth nerve toxicity with capreomycin than with kanamycin or amikacin³¹. Hence when there is similar *in vitro* activity, capreomycin is used preferably in patients 60 years or older.

Para-Aminosalicylic Acid (PAS)

With the introduction of ethambutol and, later, rifampicin, the role of PAS in the treatment of tuberculosis was relegated to that of second-line agent. 10-12 g of PAS is usually given orally in two equally divided doses. Gastric intolerance is the most common side effect. Nearly all patients suffer gastrointestinal upset in one form or another including anorexia, nausea, vomiting, and diarrhoea. Reactions manifested by fever, rashes, pruritus and hepatic dysfunction occur in about 5 to 10 percent of patients. In some patients lymphadenopathy, joint pain and pulmonary infiltrates with eosinophilia have been reported. Most of these symptoms disappear with discontinuation of therapy⁴³. PAS can cause fluid retention from excessive sodium load in patients with congestive heart failure. Hemolytic anemia have been reported in patients with

G-6 PD deficiency. PAS partially inhibits uptake of iodine by the thyroid gland and thus can cause hypothyroidism and myxedema.

Other Antituberculosis Agents

Clofazimine

This is an antileprosy agent but has been used for treatment of pulmonary tuberculosis caused by resistant organisms, although the efficacy of this medication for the treatment of tuberculosis is unknown. The drug is supplied as 50 or 100 mg soft gelatin capsules and is given or a fly preferably after meals. Daily adult dose is 100 mg. The main adverse reaction is the orange red discolorization of the skin.

Fluoroquinolones

The most extensively studied fluoroquinolones are ciprofloxacin and ofloxacin. In animal studies, sparfloxacin was 6 to 8 times more active than ofloxacin⁴⁵. The clinical reports, although still sketchy, indicate fluoroquinolone as promising antituberculosis agent, but the development of resistant strains present a serious problem⁴⁶. The development of fluoroquinolone resistance at low drug dose emphasize that resistance can be a serious problem. The resistant strain to ofloxacin were also resistant to ciprofloxacin and sparfloxacin. It seems clear that they should be used in conjunction with other antibiotics to avoid selecting for resistant strains in the treatment of multidrug resistant tuberculosis.

Ciprofloxacin

This for the treatment of human tuberculosis is used with other second-line antituberculosis drugs for the treatment of multiple drug-resistant disease. The dosage of ciprofloxacin for the treatment of tuberculosis is not yet clearly established, but a daily dosage of ciprofloxacin 1000 to 1500mg may be recommended⁴⁷.

Ofloxacin

This has been used in association with other secondary drugs to treat multiple drug resistant tuberculosis. Sputum has been converted in some patients; some have achieved complete cure with associated resectional surgery. Because the regimens used for these patients were not standardized, and because of the association with other active drugs, the contribution of ofloxacin cannot be completely assessed. The optimum dosage of ofloxacin in the treatment of tuberculosis has not yet been established. It is reasonable to recommend that a dosage of 600 mg/day or more depending on tolerance, should be used to achieve an adequate antituberculosis effect⁴⁸.

Until further data on the effectiveness of ciprofloxacin and ofloxacin in tube rculosis a re obtained, these 2 drugs should not be considered as 'miracle drug' and an answer to multiple drug resistant tuberculosis. They should not be substituted for other antituberculosis drugs with known effectiveness, nor they be used as monotherapy. They should be used only in the last resort, as experimental drugs in combination with atleast 2 or 3 other effective secondary drugs.

Newer Macrolides, Beta Lactam Antibiotics and Rifamycin Derivatives

Other oral medications that have been used for the retreatment in patient with multidrug resistant tuberculosis include, **the new macrolide** antibiotics (clarithromycin, azithromycin), amoxicillin clavulanate, and newer rifamycin antibiotics. On the basis of the activity of clarithromycin and azithromycin against *M. avium*⁴⁹, there has been considerable interest in their potential activity against *M. tube rculosis*.

Clavulanic acid 125 mg with Amoxicillin 250 mg (" Augmentin" 375mg) produced growth inhibition in 25 of 30 strains

of *M. tuberculosis*⁵⁰. The activity against *M. tuberculosis* is enhanced by changing molar ratio of ampicillin: clavulanic acid from 1: 1 to 2 : 1⁵¹. One report suggests the potential activity of amoxicillin clavulanate in multidrug resistant tuberculosis⁵². Futher in vivo studies and clinical trials in the treatment of tuberculosis are required using clavulanic acid.

Rifabutin Is a spiropiperidyl derivative of rifamycin and has found a role in the treatment of multidrug resistant tuberculosis (MDR TB). Its dose is 300 mg OD. It is active against 30 percent of rifampicin resistant *M. tuberculosis* strains⁵³⁻⁵⁷.

CROSS RESISTANCE

Cross resistance is of great practical and clinical importance especially in retreatment regimens as it will determine the use and sequence of administration of antituberculosis drugs. Fortunately, little cross resistance is found between most antituberculosis drugs. Natural resistance to thiacetazone does not involve resistance to ethionamide and reciprocally, natural resistance to ethionamide does not imply thiacetazone resistance⁵⁸. On the other hand, acquired thiacetazone resistance often involved cross resistance to ethionamide. A further complication is seen when resistance is developed in combination therapy with isoniazid and thiacetazone⁵⁹. In this situation acquired resistance to thiacetazone need not always follow acquired resistance to ethionamide⁵⁹.

Several investigations have confirmed the cross resistance among the aminoglycosides. Although kanamycin has chemical similarities to streptomycin, it is effective against streptomycin resistant organism. Kanamycin resistant organisms, however, are resistant to streptomycin⁶⁰. Strains of *M. tuberculosis* that were resistant to kanamycin were resistant to amikacin in 50 percent cases, where as strains that were resistant to amikacin were almost always resistant to kanamycin⁶¹. Since kanamycin is in wide use in the retreatment regimen of resistant tuberculosis, amikacin may be useful in patients who have kanamycin resistant organism⁶¹. Though capreomycin is often grouped with the aminoglycosides, it is structurally unrelated and therefore exhibits no cross resistance^{60,61}. Two third strains resistant to rifampicin were also resistant to rifabutin^{53,57}. As expected the strain resistant to ofloxacin were also resistant to ciprofloxacin and sparfloxacin⁴⁶.

PREVENTION OFMDR TUBERCULOSIS

The importance of MDR TB lies in its poor response to available treatment²⁶⁻²⁹⁻³⁰. In patients who are resistant to isoniazid and rifampicin the results of treatment are very poor⁶². Second and third line drugs are considerably less effective and there is no immediate hope for the development of new drugs. The overall cure rate among patients with MDR tuberculosis is about 50%³⁴.

MDR TB is a man made problem and is thus amenable to corrective action¹. Developing countries have either no or limited access to testing for drug susceptibility. Even if such a facility was available, the cost of treatment for multidrug resistant disease is prohibitive and only hope of overcoming it is prevention⁶³. The most effective tool for preventing MDR tube rculosis is short Course Chemotherapy (Table 3). Adequate initial chemotherapy is most important in prevention. Fortunately effective drugs are available. Initial intensive phase of 2 months with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol is effective even in overcoming initial isoniazid resistance in most cases and lowered the bacterial population to such an extent that continuation phase with isoniazid and rifampicin with bacteriological control will prevent the introduction of drug resistant strains into the community. Unfortunately increasing number of patients are not completing therapy and have either ongoing or recurrent disease⁶⁴⁻⁶⁵. Problems associated with the self administration of antituberculosis medications led to

Table 3
Recommended Treatment Regimens to Prevent Emergence of MDR-TB

Category	Daily Regimen	Intermittent Regimen ^{2^A}
I	2HRZE/4HR	
(New Smear Positive Pulmonary TB, seriously ill smear negative pulmonary TB or extra pulmonary TB)	2HRZE/6HE 2HRZE/6HT	2H ₃ R ₃ Z ₃ E ₃ /4H ₃ R
II	2SHRZE/1HRZE/5HRE	2S ₃ HR ₃ Z ₃ E ₃
(Relapse Failure cases) **		1H-R,Z ₃ E ₃ /5H-R ,E ₃

*Intermittent regimens should be directly observed,

**Relapse - The patient was previously treated and considered cured from TB but now smear positive for AFB.

Failures-

- The newly diagnosed patient is smear positive at 5 months or more of ATT.
- The patient stopped treatment for more than 2 months before 5 months of chemotherapy and was smear positive at last examination.
- The patient is smear negative on entry and was found smear positive at the 2nd month sputum examination.

studies of the efficacy. Observed intermittent regimens in which medications are given thrice weekly for the entire treatment period are equally effective^{24,25}. Directly observed therapy is more effective than traditional unsupervised therapy in decreasing the frequency of primary as well as acquired resistance⁶⁶. The added expenses of the time of health care worker is compensated by savings from reduction in drug use. Moreover, the potential savings from eliminating new drug resistance is huge. Although many studies have used health care workers to perform this role, there is no reason why other responsible members of the community cannot do this.

HIV AND MDR

HIV infection is associated with increased rates of resistance to antituberculosis drugs⁶⁷. It is not HIV infection per se that is at the root of the problem of emergence of drug resistant tubercle bacilli. The association of HIV infection with increased occurrence of resistance to antituberculosis medication is logical based on our understanding of the natural history of tuberculosis. In immunocompetent host, the interval from infection to disease is usually one of many decades⁶⁸. Therefore, most HIV negative individuals who have developed active tuberculosis in the past few years were infected with organisms during an era of low rates of resistance. Clearly insufficient treatment of these patients in the past have provided a reservoir of MDR organisms that are capable of being transmitted. As a result of HIV on host response, progression of disease from the time course telescoped into months or a few years. Clinical and molecular techniques have demonstrated outbreak of primary tuberculosis within cluster of HIV infected persons^{62,69-72}. Reinfection can occur in highly immunocompromised patients⁷³. Therefore patterns of resistance to antituberculosis drugs in HIV infected patients are likely to be more reflective of recent trends in the community⁶⁷.

The mean survival time for patients who are coinfecting with HIV and MDR-TB is about 2 month from the time of diagnosis of tuberculosis⁶², with 12 month mortality rate of 61 percent as compared to 32 percent in non-HIV infected patients⁷⁴.

The majority of tuberculosis isolates in both HIV positive and HIV negative persons are susceptible to two or more primary drugs. Therefore, further development of drug resistance should be prevented by the use of Directly Observed Therapy, and the initiation of four drug therapy in all cases of proven and suspected TB.

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