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Multidrug Resistant Tuberculosis; a Pharmacological view based on Revised National Tuberculosis Control Programme DOTS-Plus Guidelines.

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***Abstract*—Directly Observed Therapy Strategy (DOTS) -Plus is a part of DOTS program that adds approach for multidrug resistance tuberculosis (MDR-TB) diagnosis, management, and treatment. WHO approved DOTS-Plus program began in 2000 and was established to encourage access to high quality second line drugs for appropriate use in MDR-TB control programs. The top priority is to prevent the emergence of MDR-TB by ensuring a low default rate of cases treated with first-line anti-TB drugs. If MDR-TB has emerged in a certain area, it should be treated in addition to improving the basic treatment. In this situation, accurate and reliable drug susceptibility testing, methods to support patients in order to ensure direct observation of complete treatment and the use of maximally effective regimens must be ensured. Second-line drugs should not be held back in patients with MDR-TB rather they have a good chance of cure with it, hence the treatment, if it is to be provided, should be optimally selected and administered. This review is highlighting the pharmacological view point of second line anti tubercular drug incorporated in DOTS-Plus therapy for MDR-TB.**

***Keywords*—DOTS-Plus therapy, DOTS, MDR-TB, Adverse drug reactions, Drug resistant**

I. INTRODUCTION

Multidrug resistance tuberculosis is defined as a form of tuberculosis (TB) due to Mycobacterium (M) tuberculosis that is resistant to at least isoniazid and rifampicin, the two most powerful anti-TB drugs. This form of TB was documented in nearly every country surveyed by the World Health Organization.[1, 2]

With the implementation of the internationally accepted Directly Observed Therapy(DOTS) strategy for TB control and its essential component of standardized short-course chemotherapy (SCC), a comprehensive control strategy is available that, when followed properly, prevents the emergence of drug resistance. All currently optional regimens are based upon the first-line drugs isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin.[3]

Unfortunately, some of the same principles promoting resistance in patients in the 1950s remain intact and prevalent today, in combination with other new factors: lack of adherence to treatment, use of low quality drugs, improper diagnosis of TB patients, and lack of use of standard SCC.[4]

It is known that, MDR-TB patients are resistant to at least the two anchor drugs of SCC, a supplement to the DOTS strategy is now needed for the management of these patients. This is further supported by evidence showing that SCC offers cure rates of on average 52% and 29% in new MDR-TB patients and re-treatment MDR-TB cases, respectively.[5]

To address MDR-TB in low- and middle-income settings, the World health organization (WHO) and its partners created "DOTS- Plus for MDR-TB" a management strategy built upon the foundation and principles of DOTS. The first WHO endorsed DOTS-Plus programmes began in 2000. At that time, the Green Light Committee (GLC) was established to promote access to high quality second-line drugs for appropriate use in TB control programmes.[6]

Magnitude of the MDR-TB problem in India

Data from studies conducted by Tuberculosis Research Centre (TRC) and National Tuberculosis Institute (NTI), have found MDR-TB levels of less than 1% to 3% in new cases and around 12% in re-treatment cases. [7, 8]

Revised National Tuberculosis Control Programme (RNTCP) has recently undertaken two; community based state level drug resistance surveillance (DRS) studies in Gujarat and Maharashtra. These surveys have

been conducted as per a common generic protocol based on internationally accepted methodology and have estimated the prevalence of MDR-TB to be about 3% in new cases and 12-17% in re-treatment case.[9]

Causes of drug-resistant tuberculosis

Table.1 summarizes the common causes of inadequate treatment. However it should be stressed that MDR-TB is a man-made phenomenon – poor treatment, poor drugs and poor adherence lead to the development of MDR-TB.[4] (fig.1)

Table.1 Common causes of inadequate treatment

Providers/Programmes: Inadequate regimens	Drugs: Inadequate supply/quality	Patients: Inadequate drug intake
-Absence of guidelines or inappropriate guidelines -Non-compliance with guidelines -Inadequate training of health staff -No monitoring of treatment -Poorly organized or funded TB control programmes	-Non-availability of certain drugs (Out of stock or delivery disruptions) -Poor quality -Poor storage conditions -Wrong dosages or combination	-Poor adherence (or poor DOT) -Lack of information -Non-availability of free drugs -Adverse drug reactions -Social and economic barriers -Malabsorption -Substance abuse disorders

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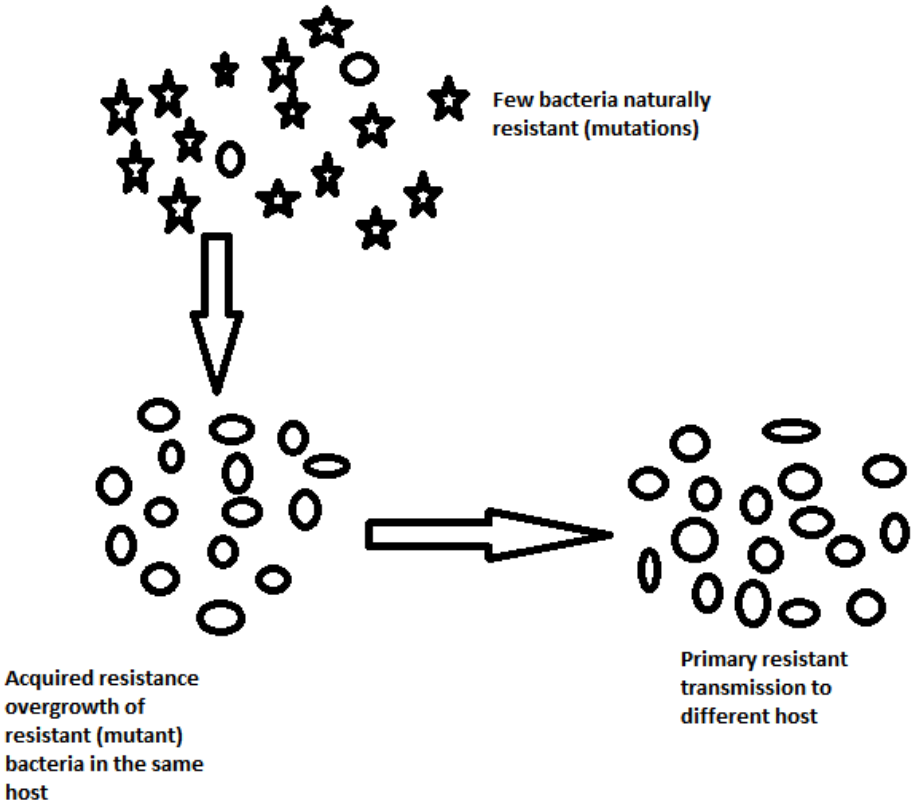

Fig.1 Acquired and primary resistance mechanism.

The RNTCP views the treatment of MDR-TB patients as a "standard of care" issue. Recognizing that the treatment of MDR-TB cases is very complex, the treatment will follow the internationally recommended DOTS-Plus guidelines and will be done in designated RNTCP DOTS-Plus sites.

DOTS-PLUS: Category IV regimen for MDR-TB

RNTCP will be using a Standardized Treatment Regimen (Cat IV) for the treatment of MDR-TB cases under the programme. Cat IV regimen comprises of 6 drugs (Kanamycin, Ofloxacin, Ethionamide, Pyrazinamide, Ethambutol and Cycloserine) during 6-9 months of the Intensive Phase and 4 drugs (Ofloxacin, Ethionamide, Ethambutol and Cycloserine) during the 18 months of the Continuation Phase. P-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any bactericidal drug (Kanamycin, Ofloxacin, Ethionamide and Pyrazinamide) or 2 bacteriostatic (Ethambutol and Cycloserine) drugs are not tolerated .[9]

Table.2 DOTS compared to DOTS-Plus Strategy

DOTS	DOTS-Plus
DOTS prevent emergence of drug resistant TB and MDR-TB	DOTS –Plus design to cure MDR-TB using second line drugs.
Make primarily use of 1st line drugs that are less expensive.	Make use of 2nd line drugs that are more toxic and expensive, difficult to treat, less effective to administrate and often poorly tolerated.
	DOTS- Plus needed in area where MDR-TB has emerged due to previous inadequate TB control.
	DOTS-Plus only recommended in setting where DOTS strategy is fully in place to prevent against the development of further drug resistance.

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Drug dosages and administration

All drugs should be given in a single daily dosage under directly observed treatment (DOT) by a DOT provider (Table.3). All patients will receive drugs under direct observation for 6 days of the week. On the 7th day (Sunday) the oral drugs will be administered unsupervised whereas injection kanamycin will be omitted. If intolerance occurs to the drugs, ethionamide, cycloserine and PAS may be split into two dosages and the morning dose administered under DOT. The evening dose will be self-administered. The empty blister packs of the self-administered doses will be checked the next morning during DOT. Pyridoxine at a dose of 100mg should be administered to all patients on an RNTCP Category IV regimen.

Table.3 Dosage and weight band recommendations

Drugs	16-25 Kgs	26-45 Kgs	>45 Kgs
Kanamycin	500 mg	500 mg	750 mg
Ofloxacin (Levofloxacin)	400 mg (200 mg)	600 mg (500 mg)	800 mg (750 mg)
Ethionamide	375 mg	500 mg	750 mg
Ethambutol	400 mg	800 mg	1000 mg
Pyrazinamide	500 mg	1250 mg	1500 mg
Cycloserine	250 mg	500 mg	750 mg
PAS	5gm	10gm	12gm
Pyridoxine	50 mg	100 mg	100 mg

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Monitoring for early detection of adverse reactions

Close monitoring of patients is necessary to ensure that the adverse effects of Category IV anti-TB drugs (DOTS-Plus regimens) are recognized early by the DOT provider (table.4).[10] DOTS makes it possible to closely monitor patients and addresses the following:

Monitoring for early detection of adverse reactions

Commonly encountered adverse reactions with second line drugs

Strategies for managing adverse reactions.

Table.4 Common adverse reactions to the drugs used

Kanamycin (Aminoglycosides) [11,12]	Ototoxicity, nephrotoxicity, vertigo, electrolyte imbalance.
Ofloxacin (Quinolones)[13,14]	Gastro intestinal symptoms: diarrhea, vomiting, and abdominal pain, central nervous system (CNS): dizziness and convulsions, phototoxicity and photosensitivity, tendinopathy and tendinitis nephrotoxicity skin rash cardiotoxicity arthralgia
Ethambutol	Visual disturbance
Pyrazinamide	Arthralgia , hyperuricaemia , hepatitis, pruritis with or without rash
Ethionamide	Gastro-intestinal: epigastric discomfort, anorexia, nausea, metallic taste, vomiting, excessive salivation, and sulfurous belching psychiatric: hallucination and depression ,hepatitis ,hypothyroidism and goitre with prolonged administration, gynaecomastia, menstrual disturbances, impotence, acne, headache, and peripheral neuropathy
Cycloserine. [15]	CNS: dizziness, slurred speech, convulsions, headache, tremor, and insomnia , psychiatric: confusion, depression, altered behaviour, and suicidal tendency, hypersensitivity reaction
PAS	Gastro-intestinal: anorexia, nausea, vomiting, and abdominal discomfort, skin rash, hepatic dysfunction hypokalemia, hypothyroidism and goitre with prolonged administration.

Revised National Tuberculosis Control Programme, DOTS-Plus Guidelines FEB-2009
Adverse effects, suspected drugs, and management strategies

Gastro-intestinal symptoms (nausea and vomiting): This may be due to the bulk of drugs and/or due to ethionamide, PAS, pyrazinamide and ethambutol. Patients who complain of nausea or vomiting can be advised to take the drugs embedded in a banana. If vomiting persists, drugs will be administered one hour after one tablet of domperidone and/or a course of proton pump inhibitor or H2 receptor inhibitor (omeprazole, famotidine, ranitidine).

Giddiness: Giddiness could be due to aminoglycosides, ethionamide, quinolone and/or pyrazinamide. Whenever a patient complains of giddiness, over sleepiness or poor concentration, patients need to be counseled.

Ocular toxicity: Whenever a patient complains of blurring of vision or disturbance in colour vision, ethambutol should be withheld.

Renal toxicity: Common offending drug is an aminoglycoside. During treatment, blood urea and serum creatinine should be done every month for the first three months after treatment initiation and then every three months thereafter whilst injection kanamycin is being administered.

Arthralgia: The offending drugs are likely to be pyrazinamide and/or quinolones. Patients who complain of arthralgia will be prescribed paracetamol 500mg three times a day or aspirin 300mg three times a day. If there is no improvement after one week, a non-steroidal anti-inflammatory drug will be prescribed (e.g. ibuprofen 200mg three times a day).

Cutaneous reactions: If there is a generalized erythematous rash, especially if it is associated with fever and/or mucous membrane involvement, all drugs should be withheld immediately. When the rashes subside, the medications can be restarted one by one, at intervals of 2-3 days. The order of reintroduction will be ethambutol, cycloserine, ethionamide, quinolones, kanamycin and lastly pyrazinamide.

Hepatitis: This could be due to the combined effect of potentially hepatotoxic drugs such as pyrazinamide and ethionamide. If the liver function test results are abnormal ethionamide and pyrazinamide are to be withheld, and the other drugs continued.

Neurological symptoms: In case of peripheral neuropathy the common offending drugs are cycloserine and ethionamide. To prevent the occurrence of such adverse reaction, all patients on an RNTCP Category IV regimen should receive daily pyridoxine 100mg. If peripheral neuropathy develops, an additional 100mg pyridoxine will be given. In case of seizures the offending drug could be either quinolones and/or cycloserine. If a patient develops seizures these drugs will be withheld and the patient will be referred to a neurologist for opinion.

Psychiatric disturbances: The common offending drugs are cycloserine, quinolones and/or ethionamide. In cases of suicidal tendencies and other psychiatric disturbances, the first offending drug is cycloserine, followed

by ethionamide and quinolones. These drugs will be withheld and further management of the patient will be done in consultation with the psychiatrist. [16]

Vestibulo-auditory disturbances: Offending drug is usually the aminoglycosides. Patient may present with tinnitus, unsteady gait or loss of hearing. Aminoglycoside will be withheld and patient referred for a specialist opinion.

Hypothyroidism: The offending drugs are usually PAS and/or ethionamide and the combination of these drugs may increase the possibility for the same. Patients may present with slowing of activities, puffiness of face and/or thyroid swelling. Patients need to be evaluated for hypothyroidism and if present, may be treated with thyroxin.

MDR-TB in special situations

DOTS-Plus (MDR-TB) in pregnancy: teratogenicity has been demonstrated in only a few of the drugs used to treat MDR-TB, all except ethambutol have uncertain safety information available. This all makes treating MDR-TB during pregnancy very challenging

All women of childbearing age who are receiving MDR-TB therapy should be advised to use birth control measures because of the potential consequences for both mother and fetus resulting from frequent and severe adverse drug reactions. It should be remembered that oral contraceptives might have decreased efficacy due to vomiting and drug interactions with MDR-TB drugs. [17,18,19]

MDR-TB with HIV co-infection

The treatment of HIV positive individual with MDR-TB is the same as for HIV negative patients. However treatment is more difficult and adverse events more common. (table.5)

Table.5 DOTS-Plus regimen's Interaction potential with antiretroviral drugs:

DOTS-Plus regimen's drug classes	Protease inhibitor	NNRTIs	NRTIs
Aminoglycosides	Interactions unlikely. Use standard doses but monitor renal function.	Interactions unlikely Use standard doses but monitor renal function	Interactions unlikely Use standard doses but monitor renal function
Thioamides:	Risk of hepatoxicity with tipranavir and darunavir.	Risk of hepatoxicity with Efavirenz and nevirapine.	No studies have been performed, interactions difficult to predict.
Cycloserine	No studies have been performed	Monitor for psychiatric morbidity with efavirenz.	No studies have been performed
Fluoroquinolone	Interactions with ofoxacin, levofoxacin or gatifoxacin Are not predicted. Cause prolongation of the QT interval and should be used with caution with other agents that do the same, including PIs.[20]	Cause prolongation of the QT interval and should be used with caution with other agents that do the same, including efavirenz.[21]	Oral absorption is reduced by buffered drugs.No studies have been performed, interactions difficult to predict.
PAS:	No studies have been performed but interactions unlikely.	No studies have been performed But interactions unlikely.	No studies have been performed But interactions unlikely.

NNRTIs, non nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor. Other possible reinforcing drugs (Third line drugs)

Amoxicillin with clavulanic acid: Beta-Lactam antibiotics have had a very limited role in the treatment of TB because mycobacteria produce beta-lactamase. Amoxicillin with clavulanic acid has been used at high doses in multi drug regimens against TB with some success. [22] Amoxicillin is commonly used in individuals with HIV infection and interactions with antiretroviral are unlikely. The addition of a beta-lactamase inhibitor to amoxicillin greatly improves its in vitro activity against M. tuberculosis.[23]

Clarithromycin: a semi-synthetic, second generation macrolide, clarithromycin, is effective against Mycobacterium avium-complex, and other NTM (Non-tubercular mycobacteria) including M. para tuberculosis. It is also recommended in the treatment of infections caused by Mycobacterium marinum and Mycobacterium

fortuitum complex. It has been shown to cause a reduction in the bacillary load and clinical improvement of M. avium disease in AIDS patients. When administered orally it undergoes first- pass metabolism so that the bioavailability is 55%. It can also be given intravenously. Interactions between Clarithromycin and several antiretroviral have been studied. Simultaneous co-administration of Clarithromycin reduces zidovudine concentrations, but no reduction is seen if Clarithromycin and zidovudine are given at least 2hrs apart. [24]

Linezolid : Linezolid is a new synthetic antibacterial agent of the oxazolidinone class, which has recently been used in Successful regimens against MDR-TB.[25] However, long term toxicities are concerning. Linezolid can cause reversible myelosuppression [26,27] and should be used cautiously in patients with preexisting cytopaenias, including those with anemia on zidovudine. Prolonged courses of linezolid have been associated with lactic acidosis and optic or peripheral neuropathy and appear to inhibit mitochondrial protein synthesis. [28,29,30] It would therefore be advisable not to co-administer other drugs, which suppress mitochondrial activity such as didanosine, stavudine, and to a lesser extent zidovudine.

Clofazimine: Clofazimine is a substituted iminophenazine bright-red dye that inhibits mycobacterial growth and binds preferentially to mycobacterial DNA causing inhibition of transcription. The MlCs of clofazimine against M. tuberculosis have not been published. Adverse reactions include discoloration of the skin, gastrointestinal upset, severe and life-threatening abdominal pain and organ damage caused by clofazimine crystal deposition, and asymptomatic discoloration of the eye. [31, 32]

Amikacin: Amikacin, an aminoglycoside, is highly bactericidal against M. tuberculosis. It is given five days a week in a dose of 15 mg/kg/day as a single dose, usually by intramuscular injection. The major side effect of amikacin is nephrotoxicity and vestibular damage. Hearing loss, hypocalcaemia, hypokalaemia and hypomagnesaemia are other side effects. In comparison to kanamycin, it is less ototoxic and less painful. [33]

Capreomycin: Capreomycin is an aminoglycoside which is bactericidal against M. tuberculosis. It is given in a dose of 15 mg/kg/day intramuscularly with maximum of 1 Gram. It is toxic to the eighth cranial nerve, causing high frequency hearing loss in 3.2 to 9.4% of patients before vestibular dysfunction occurs. Renal toxicity is somewhat more common with capreomycin than with streptomycin, and it may be associated with electrolyte disturbances secondary to tubular damage. It is suggested that in elderly patients when there is similar susceptibility to capreomycin and amikacin, capreomycin should be used since older patients seem to experience more renal and ototoxic effects with amikacin than with capreomycin.[33]

II. CONCLUSION

DOTS is a established cost-effective TB treatment strategy. A blend of technical and managerial components, DOTS quickly makes infectious cases non-infectious and breaks the cycle of transmission. Using DOTS also prevents the development of drug-resistant strains of TB that are often fatal and very expensive to cure.[34]Multi-drug-resistant TB is both an individual misfortune and a manifestation of poor program performance. The top priority is to prevent the emergence of MDR-TB by ensuring a low default rate of cases treated with first-line anti-TB drugs. If MDR-TB has emerged in a certain area, it should be treated in addition to improving the basic treatment. In this situation, accurate and reliable dug susceptibility testing, methods to support patients in order to ensure direct observation of complete treatment, and the use of maximally effective regimens must be ensured. Patients with MDR-TB have a good chance for a cure with second-line drugs, hence the treatment, if it is to be provided, should be optimally selected and administered.[35] Second-line drugs should not be kept in reserve and the treatment observation must be ensured.

Second-line TB drugs include in DOTS-Plus strategy are characterized by varied metabolic pathways. Some of these are among the oldest antimicrobials introduced into clinical practice, others have been newly approved.

Pharmacology of second-line TB drugs is elementary to managing MDR-TB in the shadow of escalating HIV epidemic especially where patients are intolerant of first-line TB drugs. MDR-TB is emerging epidemic and its management is challenging. Further needs to be done in resource-poor settings, in which the burden of HIV/ TB co-infection is greatest. The burden of MDR-TB can be reduced by better implementation of DOTS to rapidly identify, trace and re-instate treatment in poorly adherent patients receiving first-line TB drugs. So even though we have DOTS-Plus (second line TB drugs) the crucial element of whole strategy is to strengthening of DOTS (first line TB drugs) to preclude emergence of MDR-TB.

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