Manage TB
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Lecture - 35
Management of drug resistant TB
Session 01

Welcome to the session on Management of drug resistance TB. We will have two sessions under this heading and I am Dr. Banu Rekha, scientist at the National Institute for Research and Tuberculosis.

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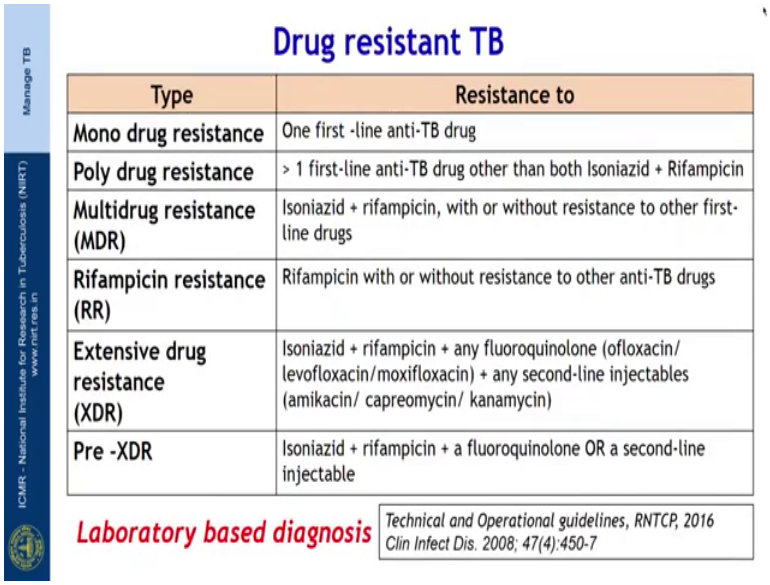

Before going to the management per say, it is important that we know about the different types of drug resistance since management of patients vary according to the type of resistance. What is mono drug resistance? Resistance to one first-line anti TB drug is known as mono drug resistant. You must have heard in previous lectures about the first-line and second-line anti TB drugs. So, in case of resistance to one of the first-line anti TB drugs it is known as mono drug resistant TB. More than first line anti TB drug resistance, other than both isoniazid and rifampicin is known as Poly drug resistant tuberculosis.

Multidrug resistance TB or M D R TB is referred to when there is resistance to isoniazid and rifampicin with or without resistance to other first-line anti TB drugs. Rifampicin resistance refers to resistance rifampicin with or without resistance to other anti TB

drugs. Extensive drug resistance or X D R TB is resistance to isoniazid plus rifampicin plus to any fluoroquinolone which may be ofloxacin, levofloxacin or moxifloxacin and to any second-line injectable, which includes amikacin, capreomycin or kanamycin.

Pre-X D R TB refers to resistance to isoniazid plus rifampicin plus a fluoroquinolone or a second-line injectable. Please remember the drug resistant TB is a laboratory based diagnosis and drug susceptibility testing have to be obtained from a quality assured laboratory based on RNTCP criteria.

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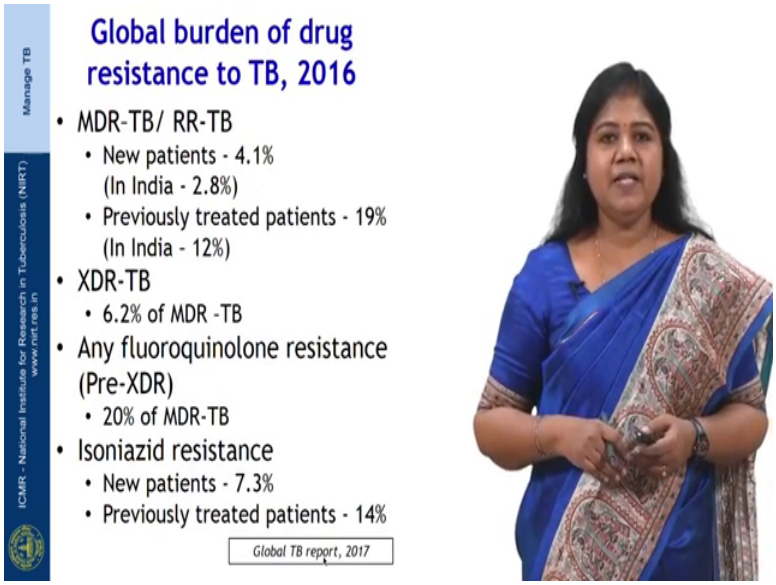

Now, let us look the global burden of drug resistance tuberculosis. Worldwide in 2016, there were about 6, 00,000 M D R and or rifampicin resistant tuberculosis cases that were reported.

Among the new patients, a Multidrug resistance or Rifampicin resistance was 4.1 percent. New patient refers to those who have never received previous anti TB treatment or less than 1 month of previous anti TB treatment. Among previously treated patients, the resistance was 19 percent. They were about 84000 M D R TB cases that were reported from India and in new patients M D R TB was about 2.8 percent and about 12 percent in previously treated patients. 6.2 percent of the M D R TB patients were X D R TB and 20 percent of M D R TB patients had any fluoroquinolone resistance in otherwise known as pre exterior. Isoniazid resistance was observed in 7.3 percent of the new patient and 14 percent of the previously treated patients.

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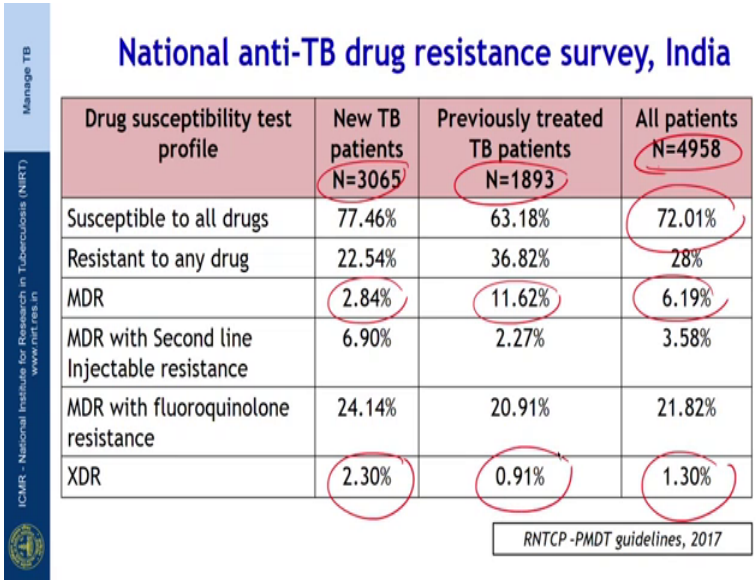

National anti-TB drug resistance survey, India

Drug susceptibility test profile	New TB patients N=3065	Previously treated TB patients N=1893	All patients N=4958
Susceptible to all drugs	77.46%	63.18%	72.01%
Resistant to any drug	22.54%	36.82%	28%
MDR	2.84%	11.62%	6.19%
MDR with Second line Injectable resistance	6.90%	2.27%	3.58%
MDR with fluoroquinolone resistance	24.14%	20.91%	21.82%
XDR	2.30%	0.91%	1.30%

RNTCP -PMDT guidelines, 2017

The results of the national anti TB drug resistance survey done in India in about 4900 patients of which 3000 where new TB patients and 1800 were previously treated patients showed that 72 percent has susceptibility to all anti TB drugs, 6 percent had a multidrug resistant TB in lab 11.6 percent among the previously treated TB patients and 2.8 percent among the new patients. The X D R TB was 1.3 percent, 2.3 percent among new TB patients and less than 1 percent in previously treated TB patients.

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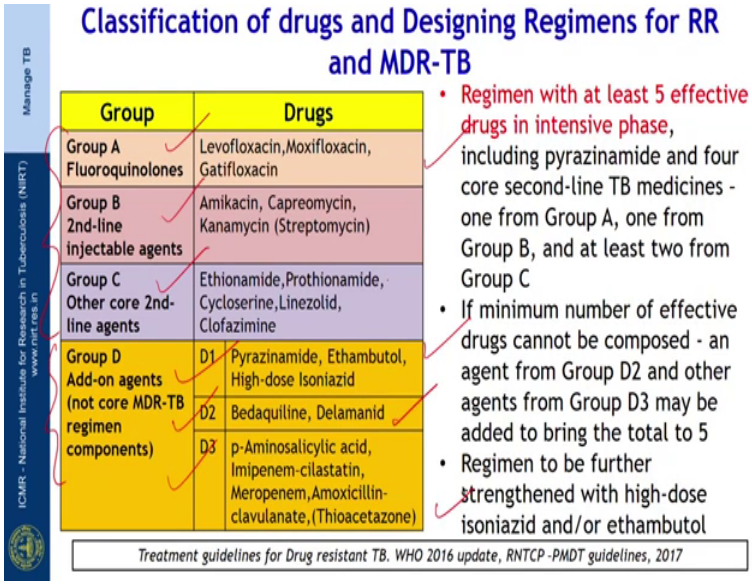

Classification of drugs and Designing Regimens for RR and MDR-TB

Group		Drugs
Group A Fluoroquinolones		Levofloxacin,Moxifloxacin, Gatifloxacin
Group B 2nd-line injectable agents		Amikacin, Capreomycin, Kanamycin (Streptomycin)
Group C Other core 2nd-line agents		Ethionamide,Prothionamide, Cycloserine,Linezolid, Clofazimine
Group D Add-on agents (not core MDR-TB regimen components)	D1	Pyrazinamide, Ethambutol, High-dose Isoniazid
	D2	Bedaquiline, Delamanid
	D3	p-Aminosalicylic acid, Imipenem-cilastatin, Meropenem,Amoxicillin-clavulanate,(Thioacetazone)

- Regimen with at least 5 effective drugs in intensive phase, including pyrazinamide and four core second-line TB medicines - one from Group A, one from Group B, and at least two from Group C
- If minimum number of effective drugs cannot be composed - an agent from Group D2 and other agents from Group D3 may be added to bring the total to 5
- Regimen to be further strengthened with high-dose isoniazid and/or ethambutol

Treatment guidelines for Drug resistant TB. WHO 2016 update, RNTCP -PMDT guidelines, 2017

Now, before going into the different types of regiments for drug resistance TB, it is important that we know about the classification of anti TB drugs. The anti TB drugs that are used for treating drug resistance TB are divided into four groups. The first three groups from group A to group C are the core anti TB drugs and group D are the Add-on anti TB agents. Group A comprises of Fluoroquinolones which are primarily Levofloxacin and Moxifloxacin. Group B comprises of second-line injectables or the aminoglycoside which are Amikacin, Capreomycin, Kanamycin and the group C, C consists of Ethionamide, Prothionamide, Cycloserine, Linezolid and Clofazimine.

The Add-on agents of the group D drugs, D 1 consists of Pyrazinamide, Ethambutol and High Dose isoniazid. D 2 or the new anti TB drugs, Bedaquiline and Delamanid and D 3 consists of Para Aminosalicylic acid, Imipenem, Meropenem group of drugs. So, how do we design a regimen with these the different group of anti TB drugs. So, the regimen has to be designed with at least 5 effective anti TB drugs in the intensive phase including pyrazinamide and 4 core second line anti TB drugs, that is one from group A, one from group B and at least 2 from group C.

If a minimum number of effective drugs cannot be composed and agent from group D 2, that is a new TB drugs and other agent from group D 3 may be added to bring the total to 5. The regimen has to be further strengthened with High Dose isoniazid and or Ethambutol.

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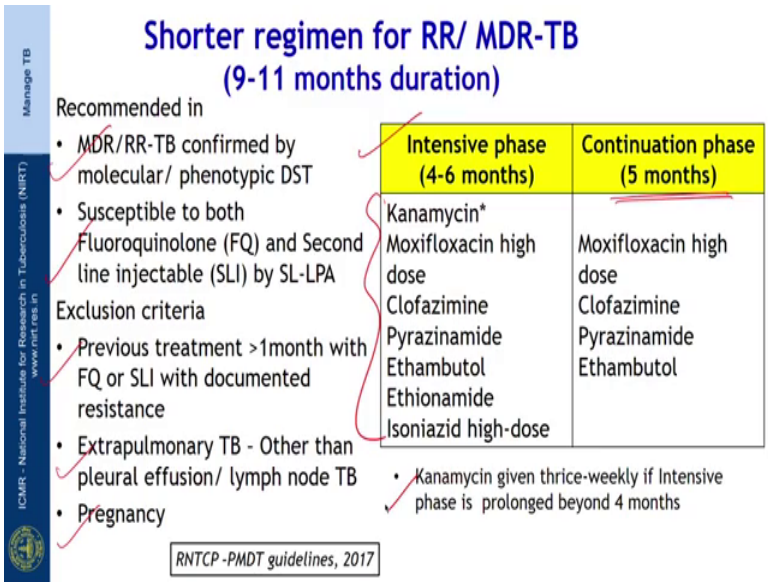

The new R N T C P programmatic management of drug resistant TB guidelines was released in late 2017 and this recommends different regiments according to the drug susceptibility profile. So, short regimen of 9 to 11 months duration is recommended for the treatment of Rifampicin Resistance or Multidrug Resistant Tuberculosis.

So, this regimen is recommended for patients, who have M D R or Rifampicin Resistant TB which is confirmed by molecular of phenotypic drug susceptibility testing and they must be susceptible to both fluoroquinolone and second line injectables by the second line probe assay. So, all these drug susceptibility testing and the line, line probe assay investigations would have been covered in previous lectures on diagnosis of tuberculosis. The exclusion criteria includes previous treatment for more than 1 month with fluoroquinolone or second line injectable with documentary resistance.

Extrapulmonary TB, other than pleural effusion on lymph node TB and pregnancy. So, what is the regiment? So, the regiment consists of an intensive phase of 6 to 9 months duration. So, the drugs are Kanamycin, high dose Moxifloxacin, Clofazimine, Pyrazinamide, Ethambutol, Ethionamide and high dose Isoniazid. The continuation phase is for a 5 months duration. This consists of Moxifloxacin high dose, Clofazimine, Pyrazinamide and Ethambutol. If the kanamycin has to be extended beyond 4 months, it has to given be given thrice weekly.

So, all these drugs for the entire duration of 9 to 11 months have to be given daily. So, shorter M D R TB regimens is also recommended for children and dose with and TB patients are HIV positive. The recommendation comes from published data and nearly 1000 patients from observational studies done in 9 countries of Sub Saharan Africa, Bangladesh, Uzbekistan, Swaziland, Cameroon and Niger. The patients treated with the shorter duration regimen had higher treatment success rates than those treated with the conventional longer duration regimen.

It was 89 percent versus 78 percent.

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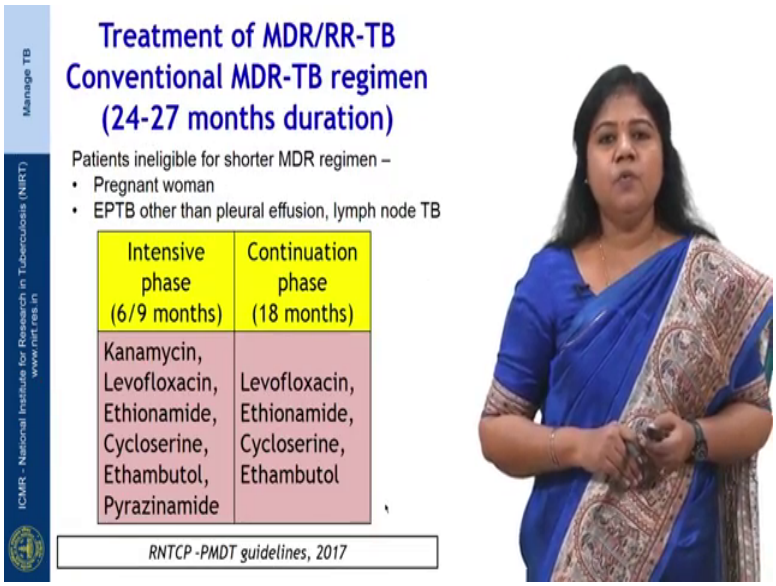

So, what do we do for patients, who are not eligible for the shorter M D R regimen? Patients ineligible for shorter M D R TB regimen which include pregnant women except Pulmonary TB other than pleural effusion or lymph node TB are treated by the conventional M D R TB regimen of 24 to 27 months duration. This consists of an intensive phase of 6 to 9 months duration with Kanamycin, Levofloxacin, Ethionamide, Cycloserine, Ethambutol, Pyrazinamide and the continuation phase without the injectable and Pyrazinamide. So, the continuation phase is for 18 months duration and the drugs in the continuation phase are Levofloxacin, Ethionamide, Cycloserine and Ethambutol.

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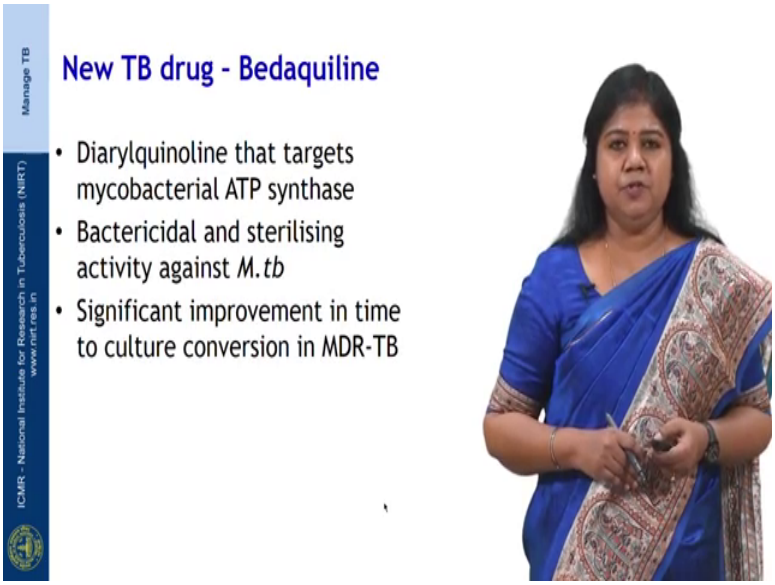

The new TB drug, Bedaquiline was approved for anti TB treatment nearly after 40 years after discovery of Rifampicin. This is a diarylquinoline that targets mycobacterial A T P synthase. It has got battery side and sterilizing activity against Mycobacterium Tuberculosis. And studies have shown that it has it causes significant improvement in time to culture conversion in Multidrug Resistant Tuberculosis.

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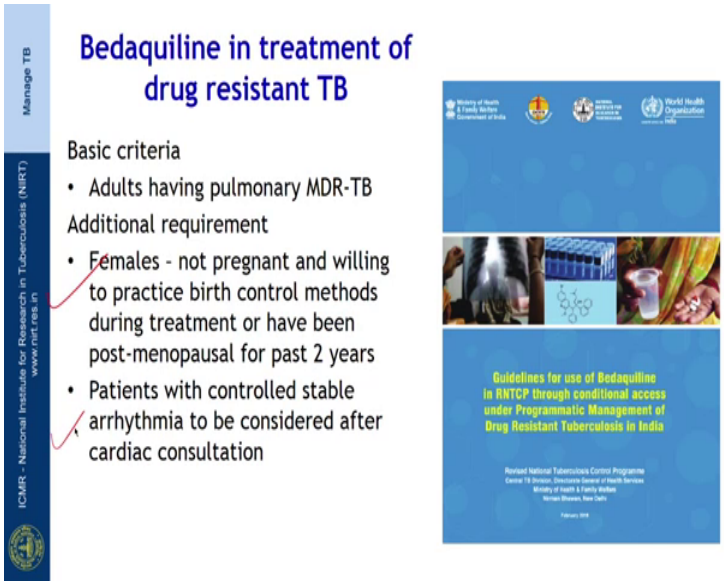

So, Bedaquiline in the treatment of drug resistant TB, initially this drug was used via the conditional access program under the R N T C P in 2016 in 6 states across the country.

Now, the drug is recommended for the treatment of drug resistant tuberculosis throughout the country. So, the basic criteria to receive Bedaquiline should be that the patient must be an adult with pulmonary M D R TB. The additional requirements include a females should not be pregnant and willing to practice birth control methods during treatment or they should have been postmenopausal for the past 2 years. Patients with controls table arrhythmia should be considered after cardiac consultation.

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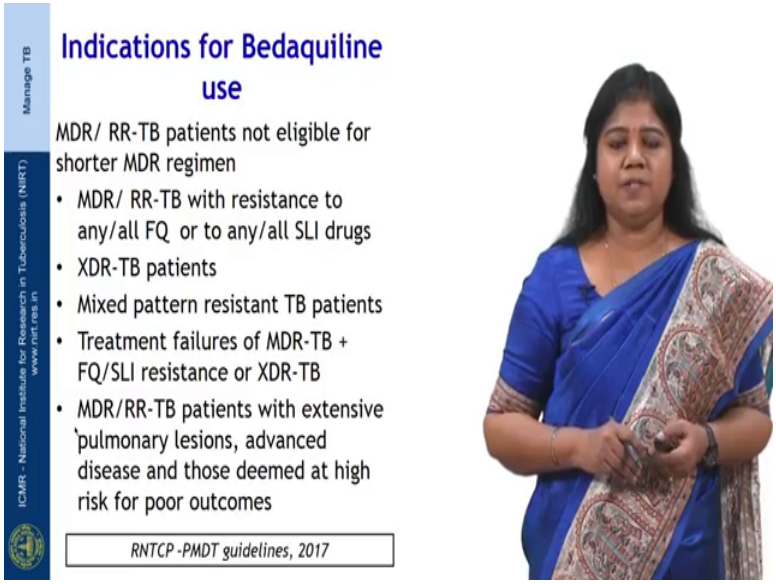

So, what are the indications for Bedaquiline use? The M D R or Rifampicin resistant TB patients who are not eligible for shorter M D R TB regimen like a M D R TB or Rifampicin resistant TB with resistance to any or all fluoroquinolone or to any or all second-line injectable drugs, the X D R TB patients, patients with mixed pattern of drug resistance, treatment failure of M D R TB along with fluoroquinolone or second-line injectable resistance or X D R TB and M D R or rifampicin resistant TB patients with extensive pulmonary lesion, advanced disease and those deemed at high risk for poor treatment outcomes. So, Bedaquiline should be considered as an option in all these group of patients.

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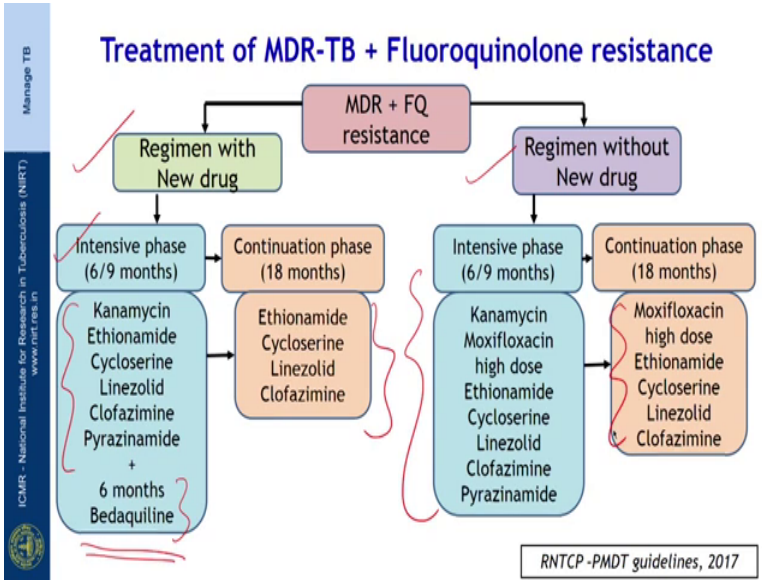

So, now, treatment of M D R TB with Fluoroquinolone resistance. So, the option is, either you treat them with the regimen with the new TB drugs that is Bedaquiline, if they are eligible. So, if you are going to consider the option of new TB drug based on the eligibility criteria for Bedaquiline, it has an intensive phase of 6 to 9 months duration with Kanamycin, Ethionamide, Cycloserine, Linezolid, Clofazimine and Pyrazinamide along with 6 months of Bedaquiline. All these drugs are given daily. In the continuation phase, it is for 18 months duration where we give Ethionamide, Cycloserine, Linezolid and Clofazimine.

Suppose the patient is not eligible for the regimen with new drug, we need to give a regiment without the new drug for this patient and this has an intensive phase of 6 to 9 months with the drugs, Kanamycin, Moxifloxacin, high dose Ethionamide, Cycloserine, Linezolid, Clofazimine and Pyrazinamide. And the continuation phase is for 18 months duration with Moxifloxacin and high dose Ethaionamide, Cycloserine, Linezolid and Clofazimine. So, how do we treat patients with M D R TB along with second-line injectable resistance?

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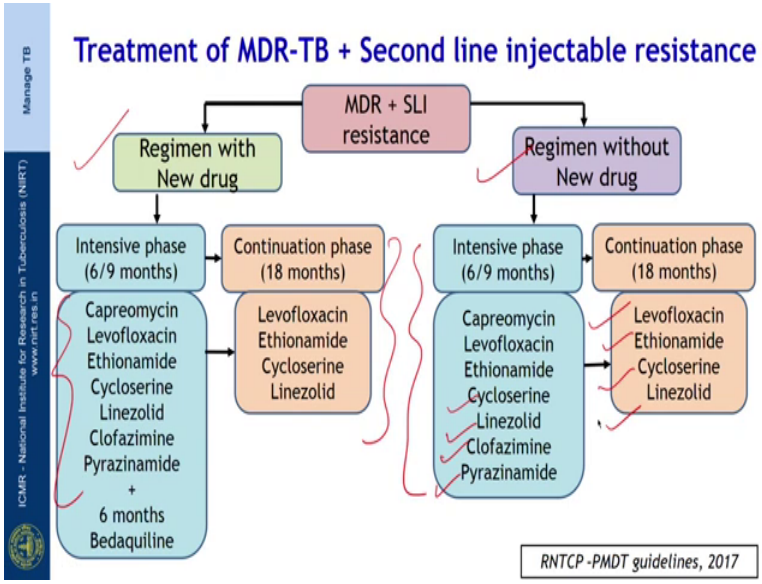

If the patient is suitable for the regimen with new drug option, then the intensive phase was 6 to 9 months will consists of Capreomycin, Levofloxacin, Ethionamide, Cycloserine, Linezolid, Clofazimine, Pyrazinamide along with 6 months of Bedaquiline. The continuation phase will be given for a duration of 18 months with Levofloxacin, Ethionamide, Cycloserine and Linezolid. If the patient is not eligible for the regiment with new drug, regimen without new TB drug will include an intensive phase of 6 to 9 months with Capreomycin, Levofloxacin, Ethionamide, Cycloserine, Linezolid, Clofazimine and Pyrazinamide and continuation phase of 18 months with Levofloxacin, Ethionamide, Cycloserine and Linezolid.

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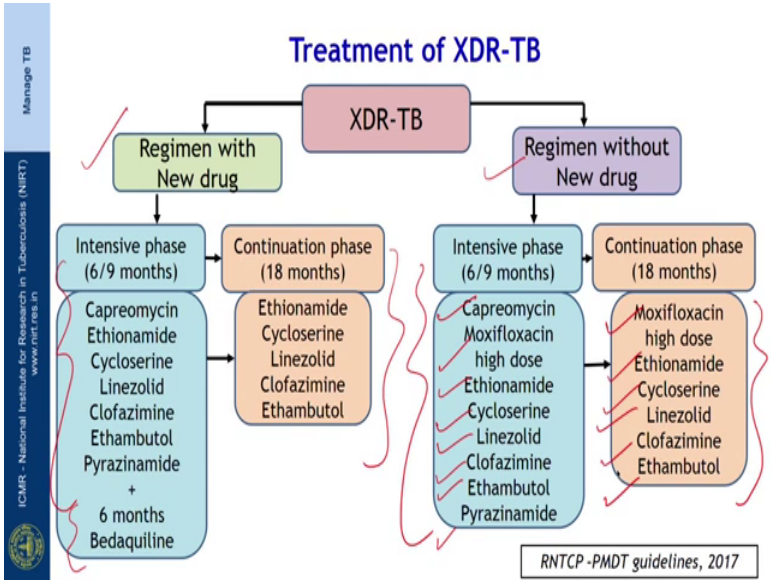

So, all these drugs have to be given for daily for the entire treatment duration. How do you treat a patient with X D R TB? So, the regimen with new drug Bedaquiline will include an intensive phase of 6 to 9 months with Capreomycin, Ethionamide, Cycloserine, Linezolid, Clofazimine, Ethambutol, Pyrazinamide along with 6 months of Bedaquiline. The continuation phase will be for 18 months duration with Ethionamide, Cycloserine, Linezolid, Clofazimine and Ethambutol.

The regimen without the new TB drug will have an intensive phase of 6 to 9 months with the drugs, Capreomycin, Moxifloxacin in high dose, Ethionamide, Cycloserine, Linezolid, Clofazimine, Ethambutol and Pyrazinamide, continuation phase of 18 months with Moxifloxacin, Ethionamide, Cycloserine, Linezolid, Clofazimine and Ethambutol. So, these drug regiments are designed based on the W H O criteria for designing of regimens for drug resistant tuberculosis.

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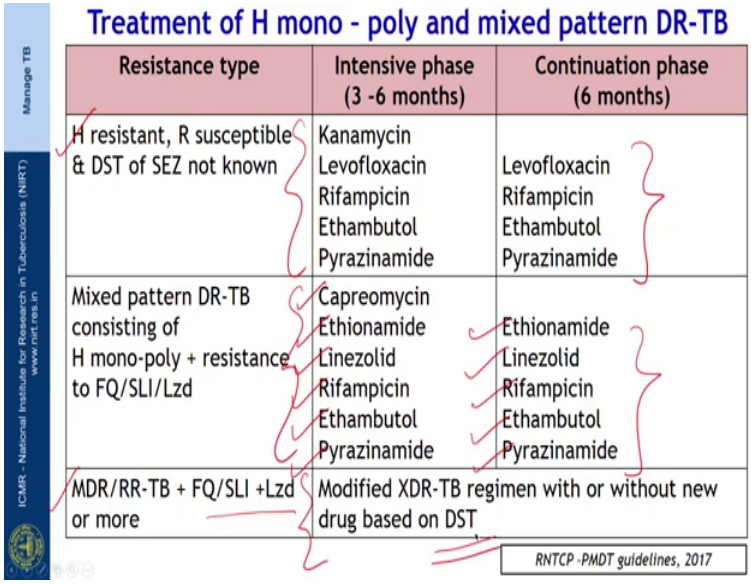

If you have to treat a patient with H, Monopoly and Mixed pattern drug resistant tuberculosis, that this chart shows the different types of regimen both in the drugs comprising in the intensive phase and in the continuation phase. H resistant tuberculosis; so, we saw in our initial slides about the burden that it is about 7 percent in new patients and 14 percent in previously treated patients.

So, these patients are treated with a 9 to 12 month regimen. So, the initial intensive phase can be for 3 to 6 months with Kanamycin, Levofloxacin, Rifampicin, Ethambutol and Pyrazinamide; a continuation phase of 6 months with Levofloxacin, Rifampicin, Ethambutol and Pyrazinamide. Patients with mixed pattern of drug resistant tuberculosis can be treated with Capreomycin, Ethionamide, Linezolid, Rifampicin, Ethambutol and Pyrazinamide and a continuation phase of 6 months with Ethionamide, Linezolid, Rifampicin, Ethambutol and Pyrazinamide. If the patient has M D R, Rifampicin Resistant TB plus fluoroquinolone or second-line injectable resistance or Linezolid resistance or resistance to more drugs, modified X D R TB regimen with or without new TB drug based on drug sustability test should be designed for them.

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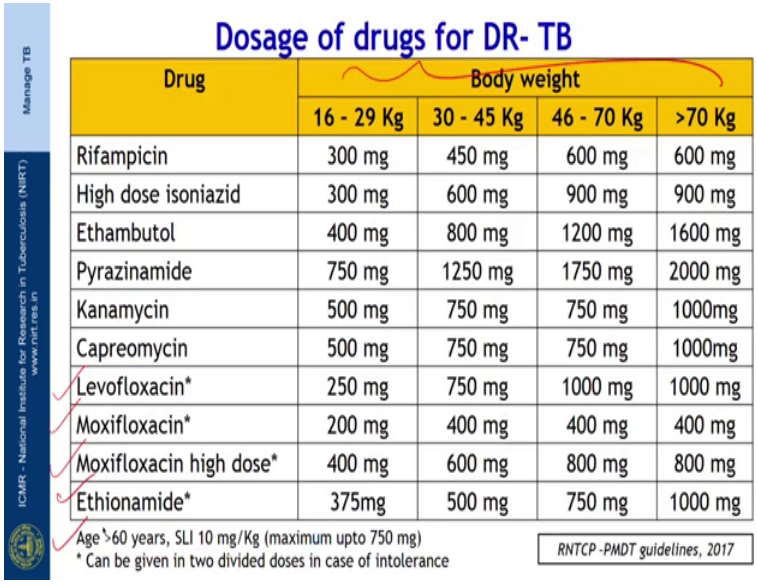

Dosage of drugs for DR- TB

Drug	Body weight			
	16 - 29 Kg	30 - 45 Kg	46 - 70 Kg	>70 Kg
Rifampicin	300 mg	450 mg	600 mg	600 mg
High dose isoniazid	300 mg	600 mg	900 mg	900 mg
Ethambutol	400 mg	800 mg	1200 mg	1600 mg
Pyrazinamide	750 mg	1250 mg	1750 mg	2000 mg
Kanamycin	500 mg	750 mg	750 mg	1000mg
Capreomycin	500 mg	750 mg	750 mg	1000mg
Levofloxacin*	250 mg	750 mg	1000 mg	1000 mg
Moxifloxacin*	200 mg	400 mg	400 mg	400 mg
Moxifloxacin high dose*	400 mg	600 mg	800 mg	800 mg
Ethionamide*	375mg	500 mg	750 mg	1000 mg

Age >60 years, SLI 10 mg/Kg (maximum upto 750 mg)
* Can be given in two divided doses in case of intolerance

RNTCP -PMDT guidelines, 2017

So, this chart shows the dosage of anti TB drugs used for treating drug resistant tuberculosis. So, there is four different weight bands based on which the drug dosage is available; 16 to 29 kilogram, 30 to 45 kilogram, 46 to 70 kilogram and more than 70 kilogram. So, based on the weight band, the dosage of the drugs will vary. So, in case of second-line injectable if the patient is aged more than 60 years, the second line injectable should be 10 milligram per kilogram daily to a maximum of about 750 milligrams.

So, drugs like Levofloxacin, Moxifloxacin and Moxi high dose, Ethionamide can be given in two divided doses in case of intolerance.

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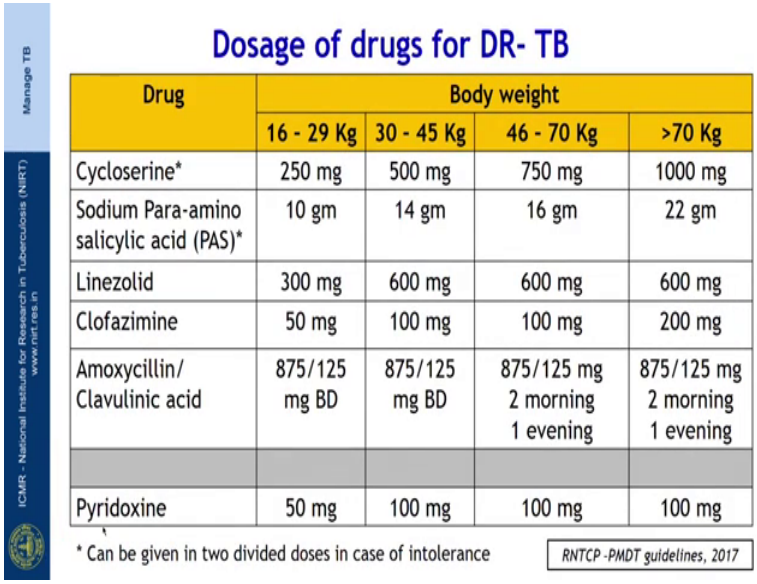

This chart shows, again shows the drugs that are used for treating the drug resistant tuberculosis like Cycloserine, P A S, Linezolid, Clofazimine and Amoxycillin; the dosages according to the different type of weight bands. So, pyridoxine is usually given along with the drugs used to treat drug resistant tuberculosis to avoid peripheral neuropathy which is side effect of certain drugs like isoniazid and linezolid.

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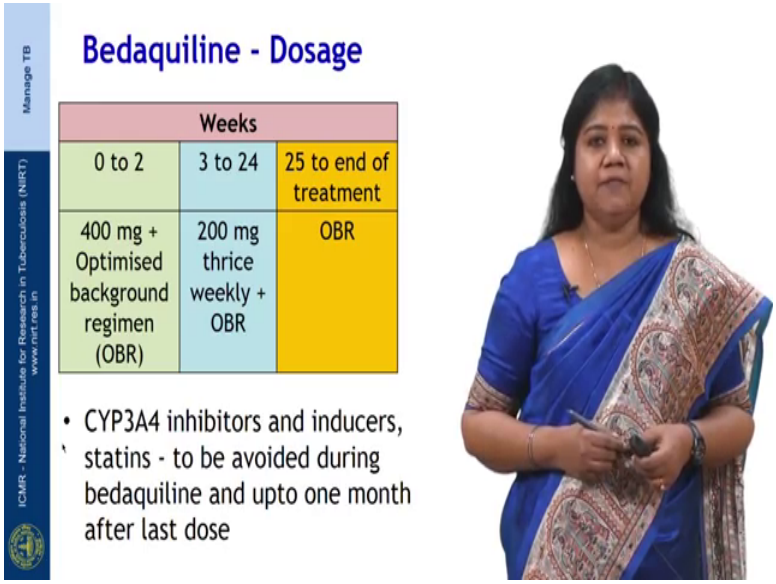

So, what is the dosage of Bedaquiline. So, Bedaquiline is given for a duration of 24 weeks or 6 months. For the first 2 weeks, the dosage is 400 milligram daily along with

the optimized background regimen. From week 3 to 24, it is 200 milligram thrice weekly. From the twenty-fifth week to the end of treatment, the background regiment alone is continued. So, this dosage of Bedaquiline is across all weight bands unlike the other anti TB drugs which vary according to the four different ways bands.

The CYP3A4 inhabitors like the azole group of drugs which include ketoconazole, fluconazole or the inducers which include phenytoin, phenobarbitone or statins which are the cholesterol lowering agents have to be avoided during the Bedaquiline dosage of 6 months duration and up to one month after the last dose of the drug to avoid potential drug-drug interactions.

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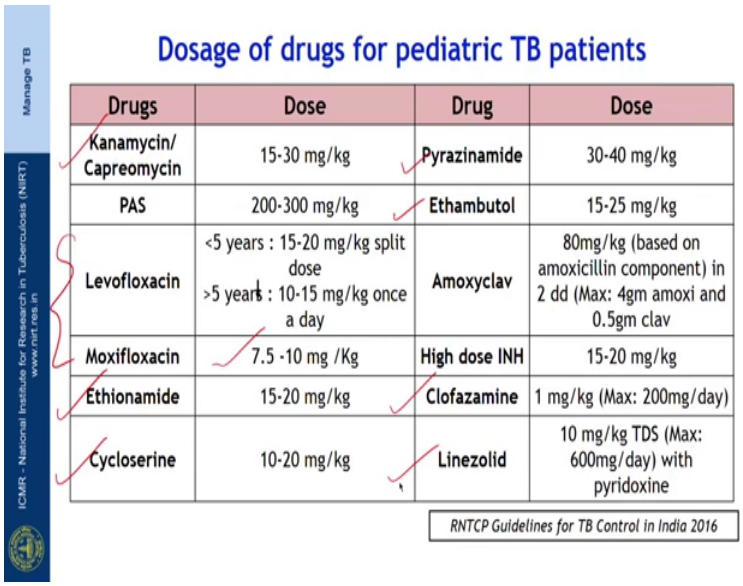

This chart shows the dosage of drugs for pediatric TB patients. So, we are going to use the second-line drugs for pediatric TB. The milligram per kilogram body weight as suggested in this chart has to be prescribed. So, aminoglycoside like Kanamycin and Capreomycin are prescribed in a dosage of 15 to 30 milligram per kilogram bodyweight.

The Quinolones, Levofloxacin and Moxifloxacin are given here. Moxifloxacin dosage is a 7.5 to 10 milligram per kilogram bodyweight. Ethionamide is 15 to 20 milligram kilogram bodyweight, Cycloserine 10 to 20 milligram kilogram per kilogram, Pyrazinamide is 30 to 40 milligram per kilogram, Ethambutol 15 to 25 milligram per kilogram and Clofazimine is 1 milligram per kilogram, Linezolid is 10 milligram per kilogram with a maximum dose of 600 milligram per day along with pyridoxine.

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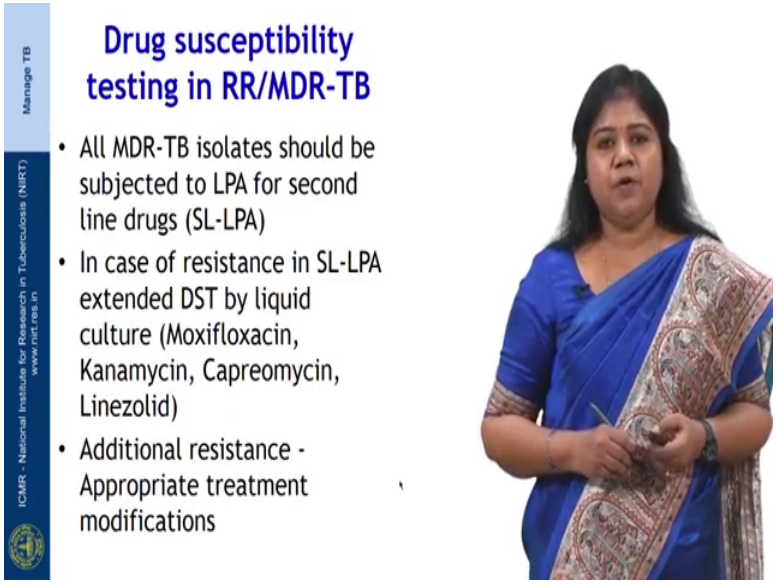

So, we need to do additional drug susceptibility testing in patients who are diagnosed with Rifampicin Resistance or Multidrug Resistant Tuberculosis. All M D R TB isolate should be subjected to line probe assay for second line drugs which include the Aminoglycoside and the Fluoroquinolone. In case of resistance in second line probe assay, extended drug susceptibility testing by liquid culture from Moxifloxacin, Kanamycin and Capreomycin and Linezolid has to be done.

In case of additional resistance, which are identified with this drug susceptibility test, appropriate treatment modifications have to be done for this patient.

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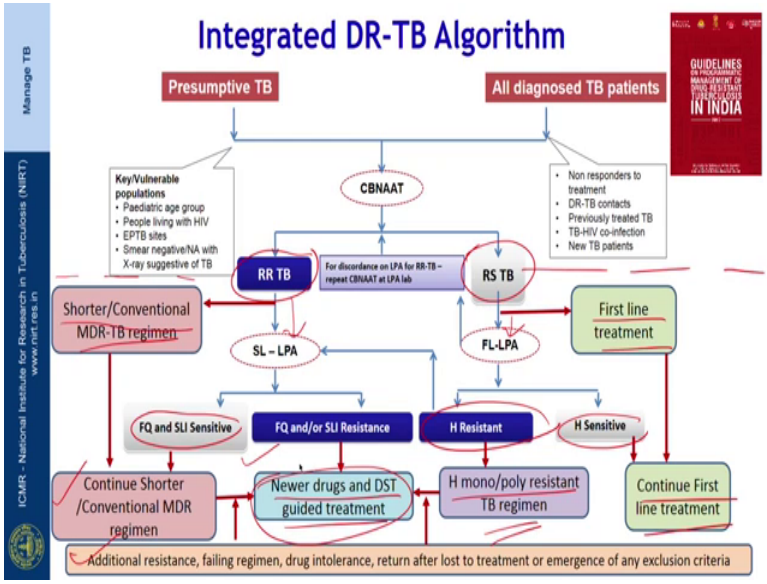

So, this flowchart summarizes the different treatment regimens that are used for treating drug resistant tuberculosis patients. So, this flow chart, you would have already seen in the lecture on approach to TB diagnosis.

Now, if you focus on the lower middle ah, middle lower part of this chart, you can see that if the patient after getting a CBNAAT test, if they are diagnosed with Rifampicin Resistant Tuberculosis, you initiate them based on eligibility criteria to a shorter or conventional M D R TB regimen.

And then this patient is subjected for second line, line probe assay test. After the test results, if the fluoroquinolone and second line injectable is sensitive, the patient has to be continued on the shorter or the conventional M D R regimen. If fluoroquinolone or second line injectable resistance is observed, then they should be evaluated for new TB drugs and D S T guided treatment. If the patient on CBNAAT has got rifampicin sensitive tuberculosis, they should be started on first line anti TB treatment and they should be tested for line probe assay for resistance to first line drugs which include isoniazid and rifampicin.

And if the isoniazid shows a resistant, then the regimen has to be modified for as pertaining to H mono and poly resistant tuberculosis. If the isoniazid comes sensitive, then we have to continue in the first line anti TB treatment. So, in case of additional resistance or failing regimen or drug intolerance or returning after lost to treatment or

emergence of any exclusion criteria, then in that case newer drugs and D S T guided treatment have to be considered in those patients.

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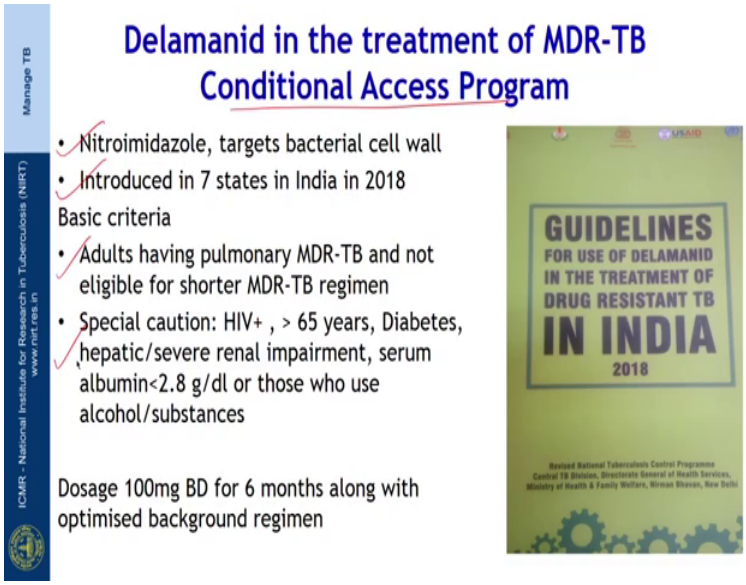

So, we talked about the Bedaquiline. So, Delamanid is another new drug that has been approved for anti TB use and granted the conditional access program under R N T C P. It is a Nitroimidazole which targets the bacterial cell wall. The it is mechanism of action is bactericidal it blocks the synthesis of mycolic acid and it also poisons a bacteria with nitric oxide which the drugs released when they are metabolized. The Delamanid is introduced in 7 states in India in 2018. The basic criteria for receiving Delamanid is the patient must be an adult with pulmonary M D R TB and not eligible for shorter M D R TB regimen.

We saw the indications for use of Bedaquiline. Similar indications apply to Delamanid also. However, special caution has to be exercised in patients with who are HIV positive more than 65 years of age, those with diabetes, those with hepatic or severe renal impairment with serum albumin less than 2.8 gram per decilitre or those whose alcohol or substances. So, Delamanid is given in combination with an optimised background regimen. The dosage of Delamanid is 100 milligrams B D for 6 months along with the optimized background regimen.

So, with this, we end the first session on a drug resistant tuberculosis where we saw the different type of drugs and the regimens for different type of drug resistance.

Thank you for your attention.