Manage TB
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Lecture – 36
Management of drug resistant TB Session 02

Welcome back to the second session on Management of drug resistant TB. In this session we will look at pretreatment evaluations and how to monitor the treatment progress including treatment outcomes.

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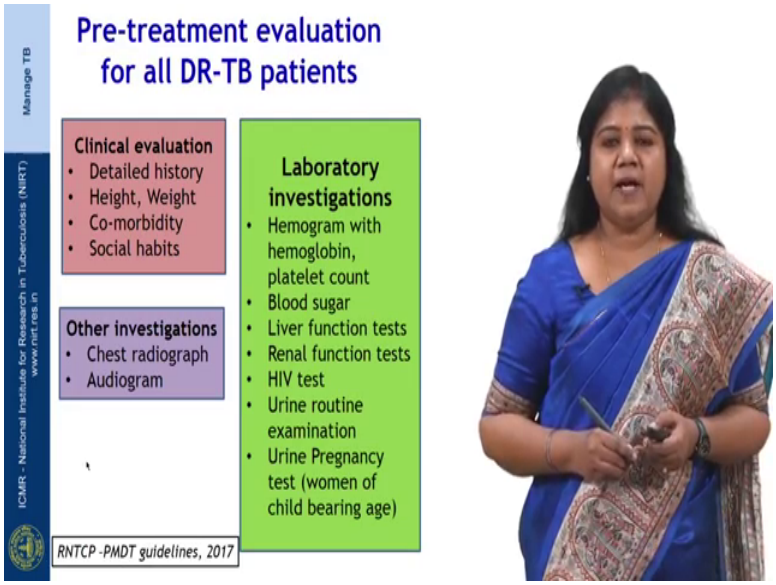

So, what are the pretreatment evaluations for all drug resistant TB patients? There should be a clinical evaluation in which a detailed history about patients symptoms is taken, including treatment with previous anti TB drugs the height and weight should be recorded, the co-morbidity especially diabetes and HIV should be documented, social habits like smoking and alcohol.

The laboratory investigations include complete hemogram with hemoglobin and platelet count blood sugar, liver function tests, renal function tests, HIV testing, routine urine examination urine pregnancy tests for women of childbearing age. The additional investigations include chest radiograph and an audiogram.

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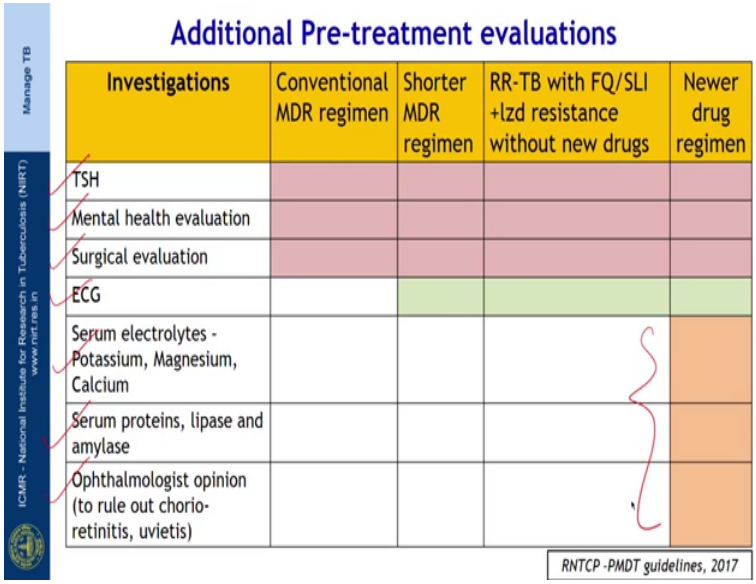

In addition to those baseline investigations, it is important to do TSH because drugs like ethionamide and pass can cause hypothyroidism. So, it is important to monitor the thyroid function. Mental health evaluation has to be done. Drugs like cyclosporine are potentially prone to cause psychiatric complications. Surgical evaluation has to be done for all patients.

So, ECG has to be done if the patient will be initiated on treatment with shorter MDR regimen or with the newer drug regimen. Serum electrolytes, serum proteins lipase and amylase and ophthalmologist opinion to rule out chorio-retinitis and uvietis has to be done, if the patient will be receiving newer drug regimen.

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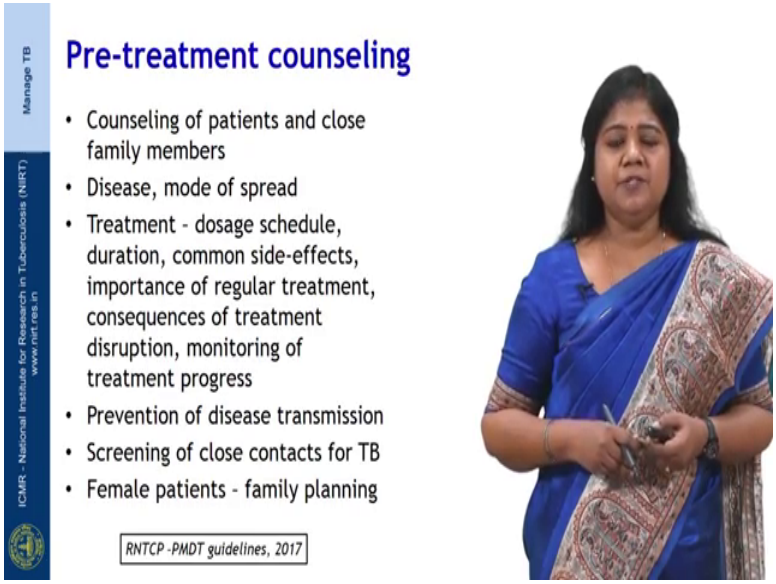

Pre-treatment counseling is very important prior to treatment initiation the treatment as we saw is for a very long duration the shorter MDR regimen is for a 9 months duration while the conventional MDR regimen and drugs for treating other sensitive resistant patterns have to be given for a duration of nearly 24 to 27 months. So, it is very important that both the patients and the close family members are appropriately counseled.

So, they must be informed about the disease, the mode of the spread of the disease, the treatment that is to be taken by the patient which includes dosage scheduled the duration for which they have to come, the common side effects of the anti-TB drugs, the importance of regular anti TB treatment and the consequences of irregular treatment and how the treatment progress will be monitored and what are the investigations that are essential for this activity.

And, it is also important to counsel them about the prevention of disease transmission like cough adequate and avoidance of spitting in the public. The screening of close contacts for TB patients have to be ensured for early diagnosis of TB and appropriate treatment. If the female patient if the MDR-TB patient is a female then there should be discussion or about the family planning methods to ensure that the patient is having appropriate contraceptive measures while taking the MDR-TB treatment.

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Supportive care has to be provided and it is very important to identify an address co-morbidities like diabetes, liver and renal disease and neurological disorder. The substance abuse which include tobacco and alcohol use appropriate counseling has to be given and interventions have to be planned accordingly.

The patients have to be linked to support schemes based on socioeconomic status because that plays a very important role in continuum of treatment nutritional assessment and support as applicable has to be provided to the patient.

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The management of drug resistant TB patients has to be done in consultation with DR-TB centers which are present at the district and at the nodal level. The treatment adherence has to be ensured by directly observed treatment which should be given logically and judiciously. The treatment supporter are also incentivized in the revised national TB control program

The information and communication technology by using frequent calls, SMS reminders, IVRS and electronic pillboxes are being explored to ensure treatment adherence.

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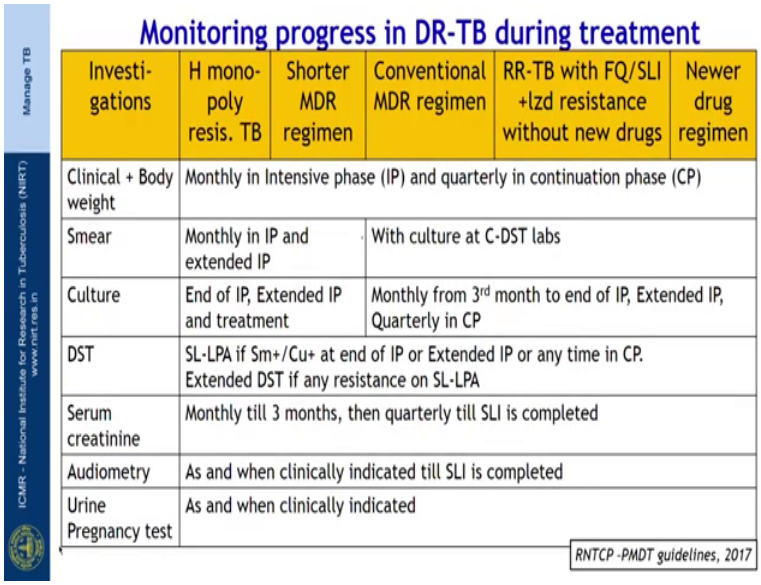

So, how do we monitor progress and treatment? So, if the investigations are basically clinical evaluation and bodyweight recording sputum, smear, culture, drug susceptibility testing, etcetera. So, as far as clinical evaluation and bodyweight recording is concerned it has to be done monthly in the intensive phase and quarterly in the continuation phase.

Sputum, smear has to be done monthly in the intensive phase and for extended intensive phase, for H mono poly resistant TB and shorter MDR regimen and for the other regimens along with culture at the culture DST labs and culture has to be done at the end of IP and extended IP and treatment, for H mono resistant TB and shorter MDR-TB regimens. While for the other regimens it is for monthly from third month to the end of intensive phase extended intensive phase and quarterly in continuation phase.

The drug susceptibility testing for second line LPA if sputum, smears or cultures are positive at the end of IP or extended IP or any time in continuation phase extended DST has to be done if any resistance on second hand LPA is detected. Serum creatinine has to be done monthly to 3 months then quarterly second line injectable is completed. Audiometry as and when clinically indicated till second line injectable is completed. Urine pregnancy test as and when clinically indicated, ok.

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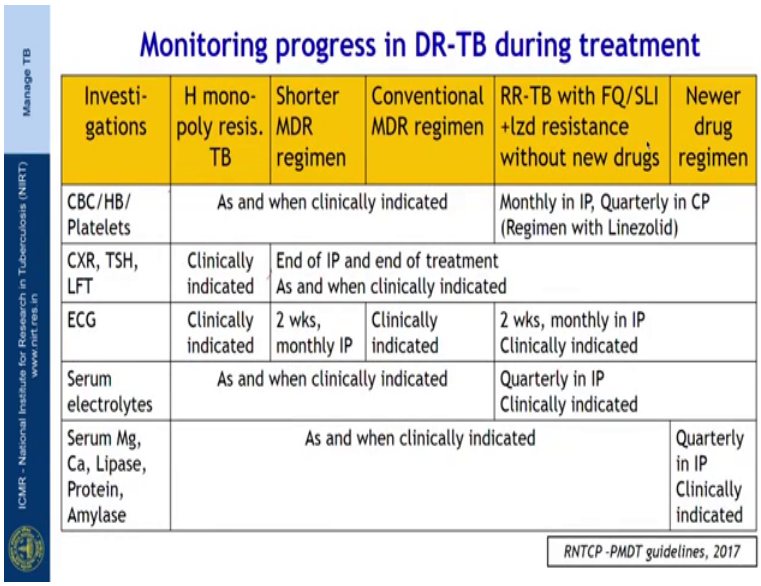

So, considering other investigations like complete blood count, hemoglobin and platelet us these can be done as and when clinically indicated. However, in regimen which consists of consists of linezolid it has to be done monthly in the intensive phase and quarterly in the continuation phase the test takes rate TSH and liver function test should be done at the end of intensive phase and end of treatment and as and when clinically indicated. ECG should be done if the regiment consists of a moxifloxacin or the new drug bedaquiline clofazimine more closely and for the other regimens is it can be done as and when clinically indicated.

So, it should be done at 2 weeks and monthly in IP the serum electrolytes should be done quarterly in IP and as and when clinically indicated if the regiment comprises of capreomycin. The serum magnesium, calcium, lipase, protein and amylase should be done quarterly in intensive phase and as and when clinically indicated if the patient is on a new drug regimen.

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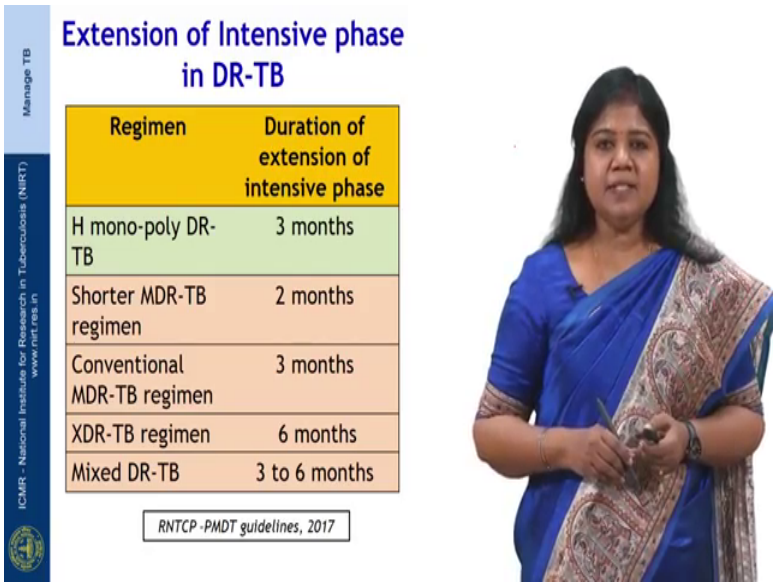

The extension of intensive phase and drug resistant tuberculosis is basically decided based on culture positivity. So, in case of h mono or poly resistant tuberculosis the duration of extensive of extension of intensive phase can be for up to 3 months, for shorter MDR-TB regimen up to 2 months, for conventional MDR-TB regimen up to 3 months, for XDR TB it can be up to 6 months and for regimen for mixed set drug resistant tuberculosis the extension of intensive phase can be up from 3 to 6 months duration.

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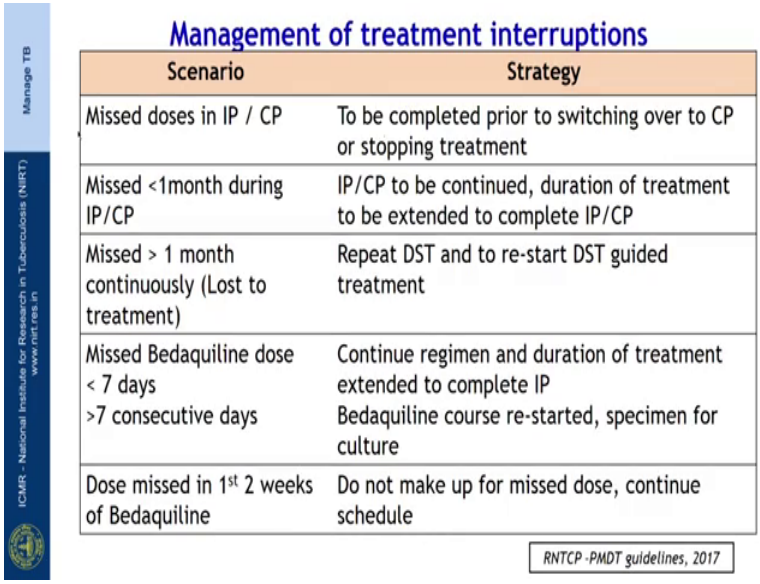

The regimen for drug resistant TB is for a longer duration. So, it is very important that we know about management of treatment interruptions. If the patient misses dose and intensive phase it has to be completed prior to switching over to continuation phase. Missed doses and continuation phase have to be completed prior to stopping treatment. If the patient misses less than one month of treatment during the intensive or continuation phase that phase has to be continued and the duration of treatment has to be extended to complete the intensive or the continuation phase. If the patient has missed more than one month of treatment continuously in other words declared as lost to treatment we should repeat the drug susceptibility testing and the treatment has to be restarted based on drug susceptibility profile.

In case of bedaquiline if the patient has missed a bedaquiline dose and the duration is for a less than 7 days the regimen has to be continued and the duration of treatment extended to complete the intensive phase. If the missed bedaquiline dose is for more than 7 consecutive days the bedaquiline dose has to be restarted and the specimen has to be sent for culture. If the dose is missed in the first 2 weeks of bedaquiline one should not make up for the missed doses and continue the treatment schedule.

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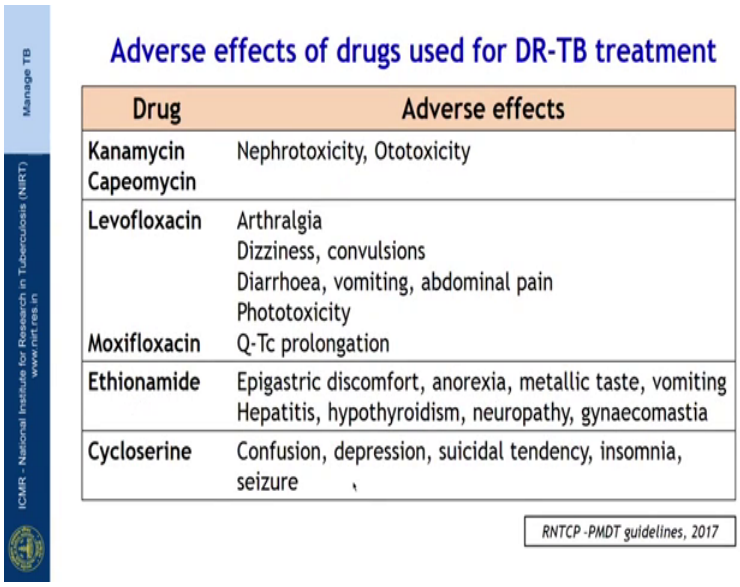

So, what are the different adverse effects of these drugs which are used to treat drug resistant tuberculosis? We have a separate session on a adverse drug reaction and its

management. I will briefly mention about the important adverse effects of the drugs that are used for treating drug resistant tuberculosis.

For so, the aminoglycosides kanamycin and capeomycin can cause nephrotoxicity and ototoxicity the fluoroquinolone levofloxacin can and the moxifloxacin can cause arthralgia, dizziness, convulsions, GI disturbances like diarrhea, vomiting and abdominal pain and photo toxicity, in addition moxifloxacin can cause Q-Tc prolongation. Ethionamide can cause gastrointestinal disturbances which include epigastric discomfort, anorexia, metallic taste, vomiting, hepatitis, hypothyroidism, neuropathy and gynecomastia. Cycloserine can cause confusion, depression, suicidal tendency, insomnia and seizure.

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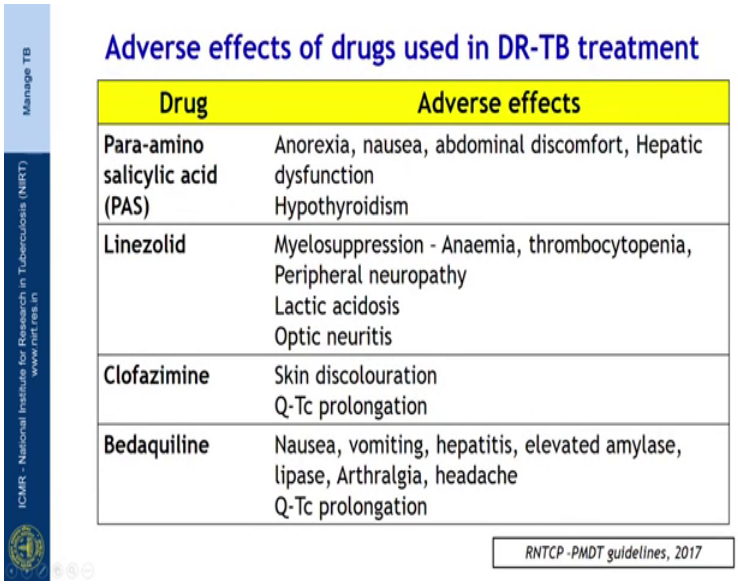

Drugs like para-amino salicylic acid can cause gastrointestinal intolerance, hepatic dysfunction and hypothyroidism. Linezolid can cause myelosuppression leading to anaemia and thrombocytopenia, peripheral neuropathy, lactic acidosis and optic neuritis. Clofazimine can cause skin discolouration and Q-Tc prolongation. The new drug bedaquiline can cause nausea, vomiting, hepatitis, elevated amylase and lipase arthralgia, headache and Q-Tc prolongation. So, these are the various adverse effects of the drugs used for treating drug resistant tuberculosis.

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So, what is the role of surgery in MDR and XDR TB? So, we saw in pre treatment evaluations surgical evaluation is one of the most important investigation that has to be done. So, if the patient has got a unilateral resectable disease and there is absence of response to treatment with effective anti TB drugs despite 6 to 9 months of regular treatment.

In case of morbid complications of parenchymal disease, which include hemoptysis and bronchiectasis or if there is reversion of culture to positive during treatment, relapse after treatment completion high risk of failure or relapse in case of high degree of resistance or parenchymal involvement surgical evaluation has to be done and surgery has to be considered for these patients.

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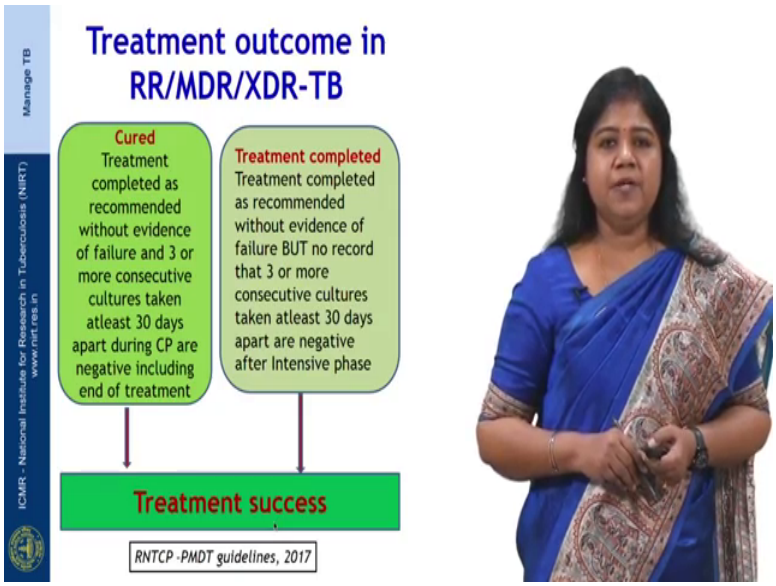

So, now let us look at the treatment outcome in rifampicin resistance MDR and XDR TB. So, what is cured? A patient is declared cured if he completes treatment as recommended without evidence of failure and 3 or more consecutive cultures taken at least 30 days apart during continuation phase are negative including the one at the end of treatment. Treatment completed refers to completion of treatment as recommended without evidence of failure, but no record that 3 or more consecutive cultures taken 30 days apart are negative after the intensive phase. So, both cured and treatment completed constitute treatment success.

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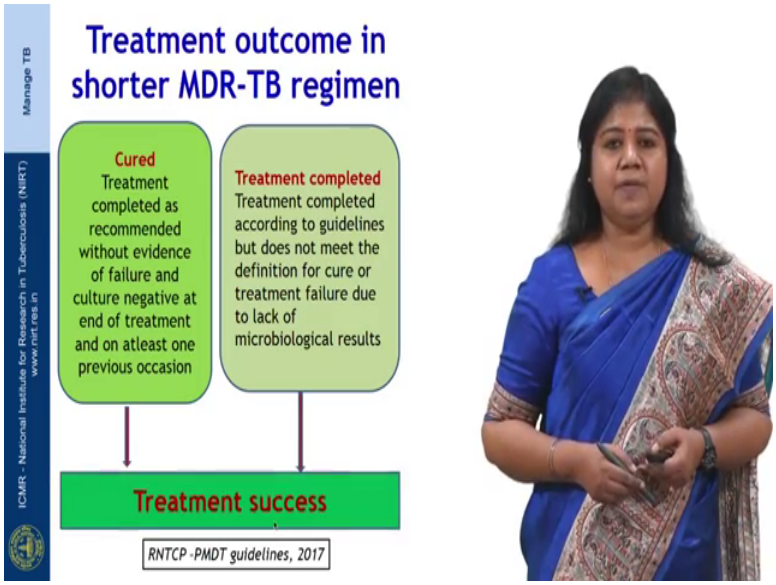

The treatment outcome as far as shorter MDR-TB regimen is concerned. So, cured is treatment completed as recommended without evidence of failure and culture negative at the end of treatment and at least one previous occasion. Treatment completed is completed treatment according to guidelines, but does not meet the definition for cure or treatment failure due to lack of microbiological results. So, these two comprise the treatment success.

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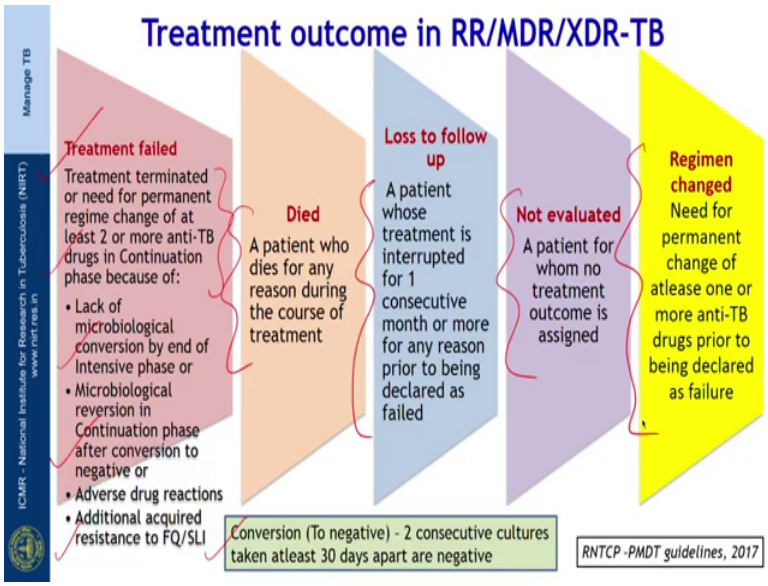

So, what are the unfavorable treatment outcomes in case of drug resistant tuberculosis? A patient is considered treatment failed if the treatment is terminated or need for permanent regimen change of at least 2 or more anti TB drugs in continuation phase because of lack of microbiological conversion by the end of intensive phase or microbiological reversion in continuation phase after conversion to negative or adverse drug reactions or additional acquired resistance to fluoroquinolone alone or second line injectable. So, the definition of conversion today negative refers to two consecutive cultures taken at least thirty days apart are negative.

A patient who dies for any reason during the course of anti TB treatment the outcome is taken as died. Loss to follow up a patient whose treatment is interrupted for one consecutive month or more for any reason prior to being declared as failure is declared as loss to follow up. A patient for whom no treatment outcome is assigned is not evaluated. Regimen change; a patient who needed permanent change of one at least one or more

anti TB drugs prior to being declared as failure so, the outcome is regimen changed for such a patient.

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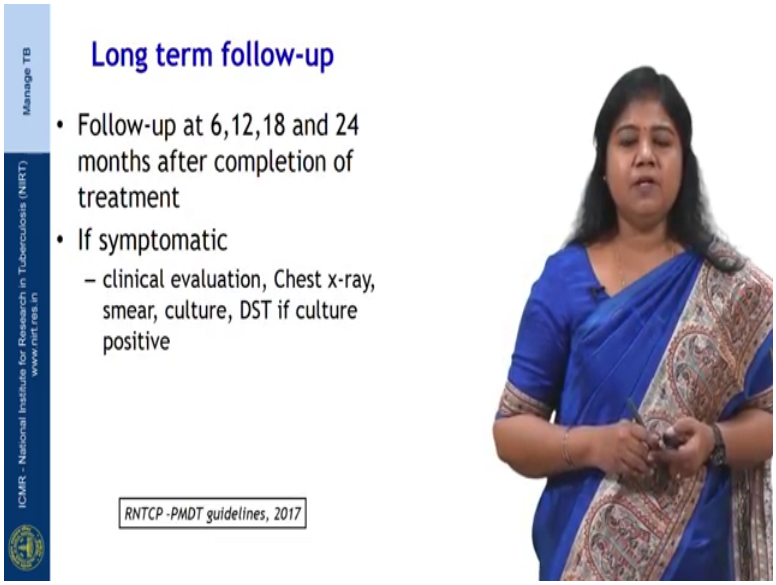

These patients have to be followed up after completion of treatment at 6, 12, 18 and 24 months. If the patient is symptomatic during the follow up period clinical evaluation, chest x-ray, smear, culture and drug susceptibility test. If culture is positive have to be done. So, if the patient has a treatment success it is very important that long term follow up for at least 2 years is done for these patients.

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Palliative care is very essential for patients who are chronically ill especially due to extensive disease if they failed XDR TB or if they have a mixed pattern drug resistance-regimen, regimen cannot be designed with new drugs or to alleviate the suffering during treatment.

So, the palliative care includes respiratory rehabilitation, relief measures from pain and other symptoms, infection control measures, nutritional support, vocational rehabilitation, preventive measures and psychosocial support.

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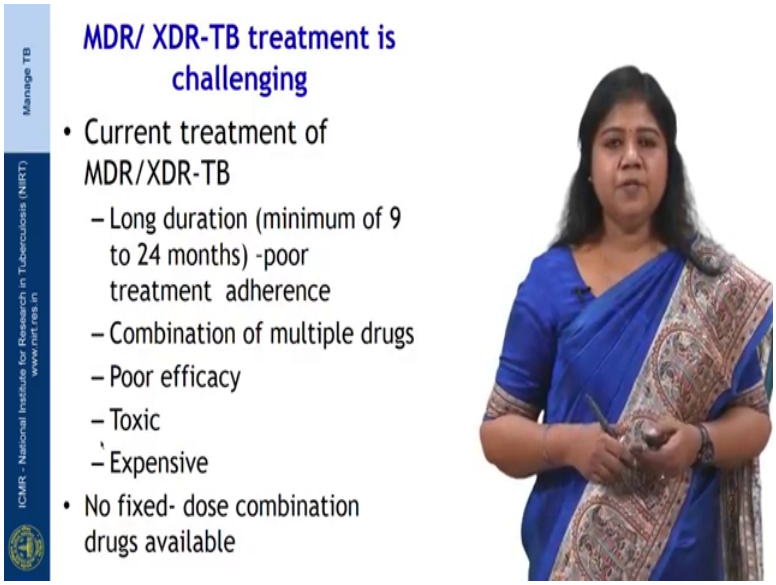

So, coming to nearly to the end of this session we must acknowledge the fact that the management of MDR, XDR TB is very challenging because the current treatment regimen is for a longer duration. The minimum treatment duration is for 9 to 24 months and this can lead to poor treatment adherence.

Moreover there is combination of multiple drugs that the patient has to swallow, which is very difficult for the patient. The drugs have been reported to have poor efficacy and they are also toxic. These drugs are more are about 4 to 5 times expensive than the cost that is used to treat drug sensitive TB patients. Moreover no fixed dose combinations are available.

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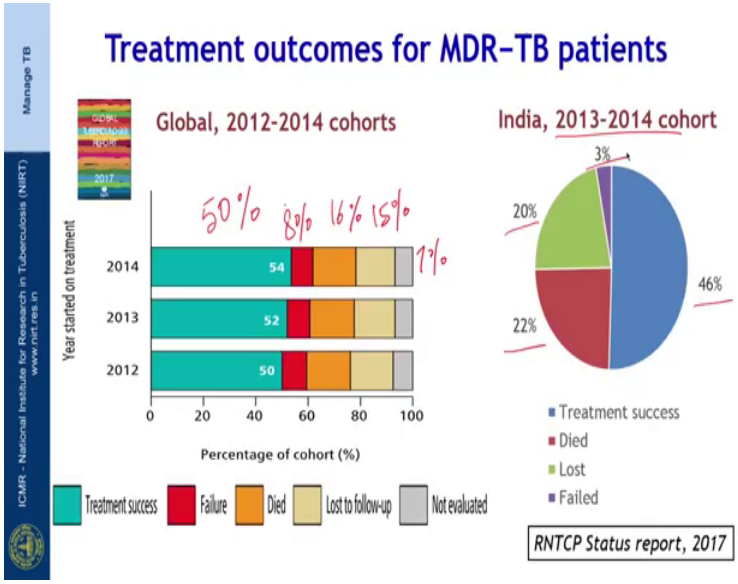

So, if we look at treatment outcomes of MDR-TB patients so, globally from 2012 to 2014 cohorts we can see that the treatment success is only about 50 percent. About 8 percent of the patients have failed the regimen, about 16 percent had died and 15 percent were lost to treatment follow up and about 7 percent were not evaluated.

So, in India according to the RNTCP status report in about 21000 patients who belong to the 2013 and 2014 cohort treatment success was 46 percent, about 22 percent had died about 20 percent were lost to follow up and about 3 percent had failed treatment. So, you can see that the success rate in MDR-TB patients is really low.

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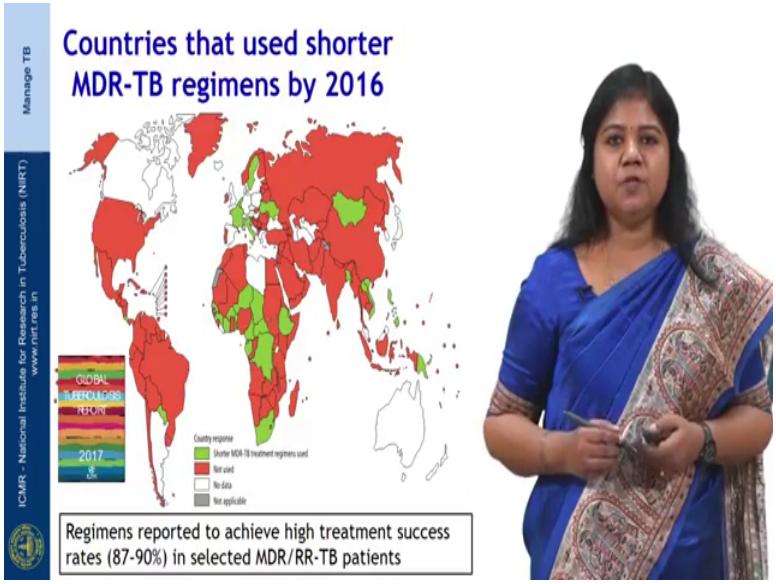

This map shows the status of the countries that had used shorter MDR-TB regiments by 20 16 the ones in green are the countries which have used a regimen. Mostly they are about 35 countries from sub Saharan Africa and Asia had used this regimen and this regimen is reported to achieve a high treatment success rate of about 87 to 90 patients in selected MDR or Rifampicin Resistant TB patients. In India this regimen has been recently recommended so, we are yet to see it is use and it is treatment success.

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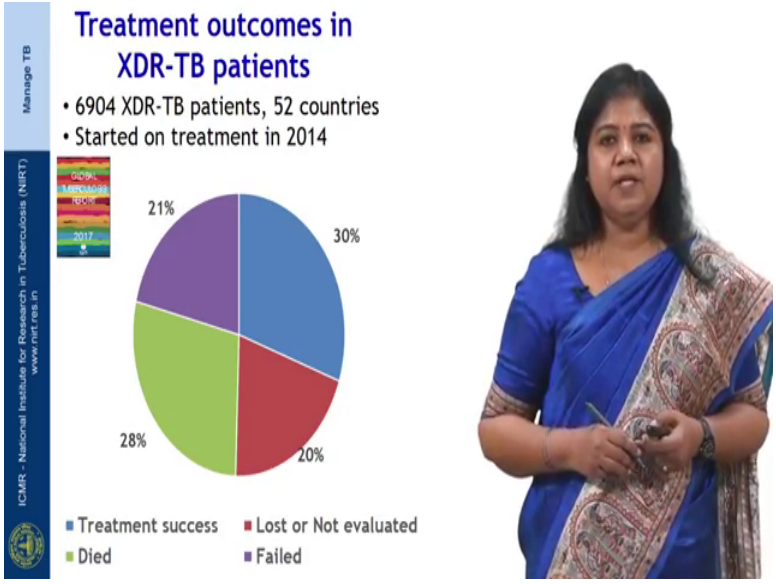

If we look at treatment outcomes of XDR-TB patients according to the global report about 6900 patients who had started on treatment in 2019 from 52 countries it has shown that the treatment success is a about 30 percent, about 28 percent had died, about 20 percent were lost or not evaluated and about 21 percent had failed treatment.

So, the treatment success of XDR-TB patient is very very low even as compared to MDR-TB patients.

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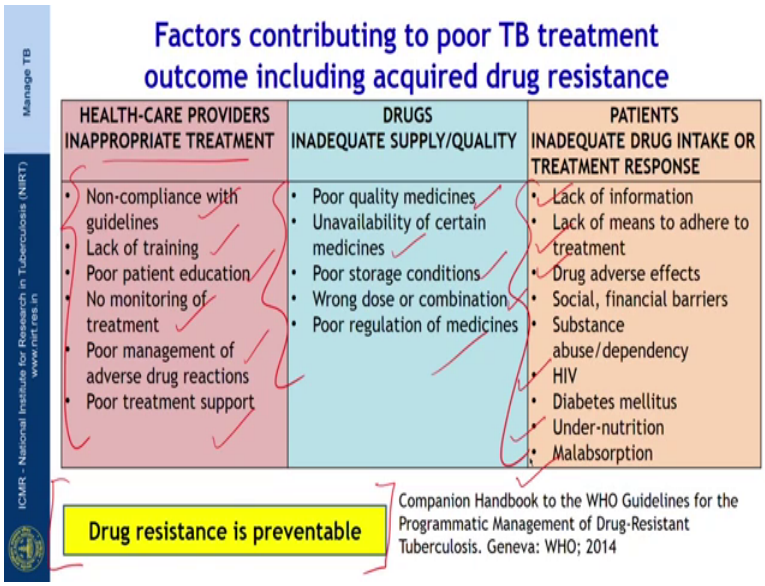

So, this is a final slide of my session which shows that drug resistant TB is preventable considering the challenges it poses in terms of management, because if you see that the factors that contribute to acquired drug resistance can be divided into three different categories. From the healthcare provider perspective it might be due to inappropriate treatment which is due to non compliance with guidelines, lack of training, poor patient education, no monitoring of treatment, poor management of adverse drug reaction and poor treatment support.

So, it is important that all these factors are addressed to prevent drug resistance in terms of drugs it may be poor quality medicines, unavailability of certain medicines, poor storage condition, wrong dosage combination or poor regulation of medicines. So, it is important that the correct combination with appropriate dosage is given for the prevention of drug resistance. From the patient perspective it might be due to lack of information that is provided, lack of means to adherent adhere to treatment, drug adverse

effects, social and financial barriers substance abuse or dependency comorbid conditions like HIV and diabetes mellitus, under-nutrition and malabsorption.

So, all these factors contribute to acquired drug resistance. So, it is very important that all these factors are addressed and drug resistance is prevented.

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So, the key messages from this two sessions are prevention of drug resistance is a priority. The treatment of drug resistant TB is less effective more prolonged expensive and toxic compared to the treatment of drug sensitive TB. Minimum treatment duration is for 9 to 20 months duration in drug resistant TB. The dosage of drugs is based on body weight.

The pre-treatment counseling is very important for these patients because of the longer duration of treatment. The monitoring treatment progress and adverse drug events is important and newer drugs and regiments are warranted to improve the treatment success among these drug resistant TB patients.

Thank you for your attention.