Manage TB
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Lecture – 31
Drugs for treating Tuberculosis and Principles of Chemotherapy
Session 01

Welcome to this session on Drugs for treating Tuberculosis and Principles of Chemotherapy. I am Dr. Rajeswari, former scientist from NIRT Chennai. Before we start this session, let us look into the definition of tuberculosis; Tuberculosis is a chronic infection, characterized by granuloma formation, affecting elderly children, all age groups affecting all the organs not only lungs; especially in the host of human beings who are immune compromised especially cell mediated immunity.

So, today's session the first half we look into the drugs that are available for treating TB and in the second half, we look into the principles of chemotherapy that govern the management.

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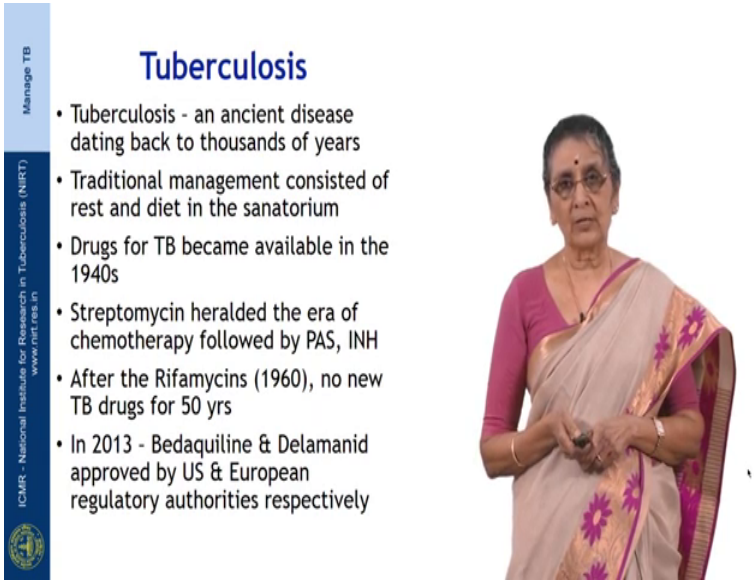

As we all aware tuberculosis is an ancient disease dating back to 1000's of years and the usual management prior to 1940 would be to give them rest adequate rest especially sanatorium line of management and give proper diet to improve the immunity of the host.

Drugs started coming in the treatment of TB from 1940 onwards and the first drug that was tried the treatment of tuberculosis were streptomycin. The famous streptomycin trials are the first chemo therapeutic trials and that showed mono therapy will be a failure and if you treat patients with a single drug they will all go into failure with resistant organisms.

Then followed the era of PAS, INH patients are treated with 2 drugs (Refer Time: 01:53) 9 INH or PAS INH or 3 drugs streptomycin, PAS and INH. This continued till the 1960's and we had a wonder drug called rifampicin and this bactericidal drug that gave a opportunity for us to treat the patient within 6 months period and that changed the picture completely.

Let us look into the number of drugs that came after 60 also. For 50 years there were not many drugs, then in the last decade there are a number of drugs that are being tried and they are in phase 2 and phase 3 trials especially bedaquiline, delamanid these two are the drugs approved by the US and European regulatory authorities.

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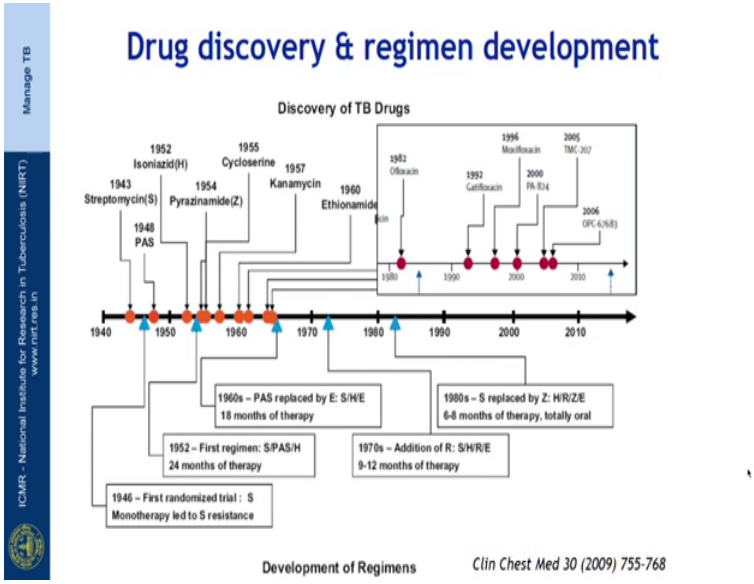

Now, this diagram clearly tells you the number of drugs and their availability in various periods. Way back started with streptomycin, PAS INH and came the pyrazinamide (Refer Time: 02:53) then rifampicin. Ooph after 60's the management totally was different because of the rifampicin and pyrazinamide they look at the regimens now. After 60's and 80's we started getting quinolones in the picture, number of quinolone

there are about 16 or 17 quinolones and about 3 or 5 are useful in the treatment of tuberculosis now currently we have bedaquiline and other drugs.

If you look at the lower half of this slide you will see the number of regiments; the earlier years in 50's and 60's it was a standard chemotherapeutic regimen consisting of 2 drugs namely INH PAS or streptomycin or and INH these regiments were given for a period of 12 to 18 months. They also had a relapse rate of more than 20 percent the cure rate was only around 50 to 60 percent.

So, there was a need to improve the treatment regimens luckily we had a rifampicin in 1960's and the picture change totally currently the line of management is used for drugs namely the rifampicin, INH, pyrazinamide ethambutol and we are able reduce the duration of treatment to 6 months and they are known as short course chemotherapy; we will look into the details in subsequent slides. Now, the recently available drugs are given here they are being tried as I told you earlier they are in phase 2 and phase 3 trials.

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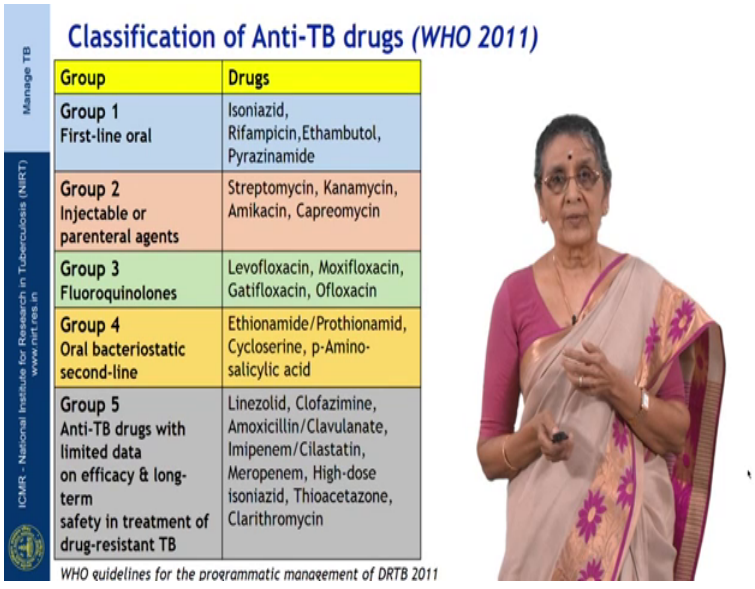

WHO classified the anti-TB drugs in 2011 as 5 groups the group; group 1 was fully oral drugs INH, rifampicin, ethambutol, pyrazinamide as I told you these are the 4 key drugs in short course chemotherapy. Group 2 consists of injectable streptomycin, kanamycin; group 3 fluoroquinolones mainly levo, maxi, gati and ofloxacin. Group 4 fully bacteriostatic second line drugs like ethionamide, cycloserine and group 5 other anti-TB drugs with limited data on efficacy, like linezolid, clofazimine etcetera.

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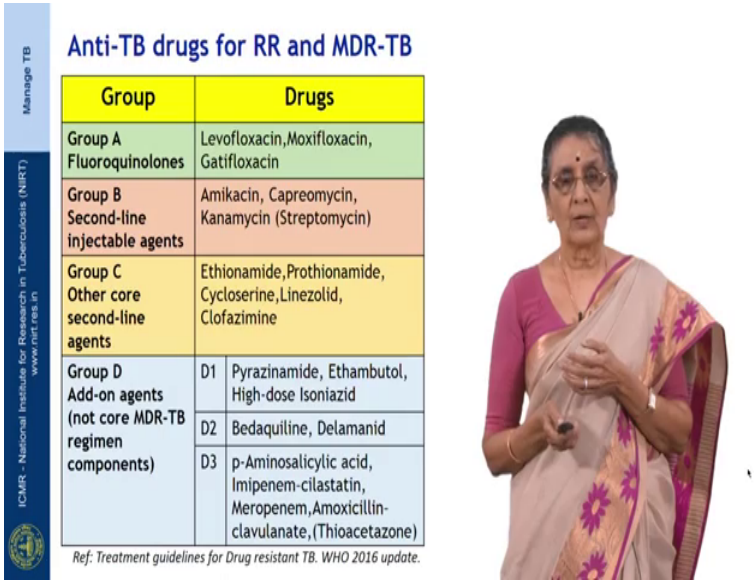

Now the anti-TB drugs for resistance that classification is slightly different, currently we have multi drug resistant tuberculosis. Now, what is multi drug resistant TB? It is bacteria that are resistant to 2 key drugs in the chemotherapy namely rifampicin and INH to bactericidal drugs; when patient developed organisms resistant to both the rifampicin and INH they are called them MDR-TB patients.

And the classification here is slightly different as you can see group A drug is fluoroquinolones, group B is second line drug injectable drugs like amikacin, group C is other second line agents like ethionamide, prothionamide, group D once again its divided into D 1, D 2, D 3 consisting of pyrazinamide, ethambutol, bedaquiline, delamanid and other drugs.

Now, in MDR-TB the regiments are being designed including all these 4 groups of drugs that will be a separate session for you.

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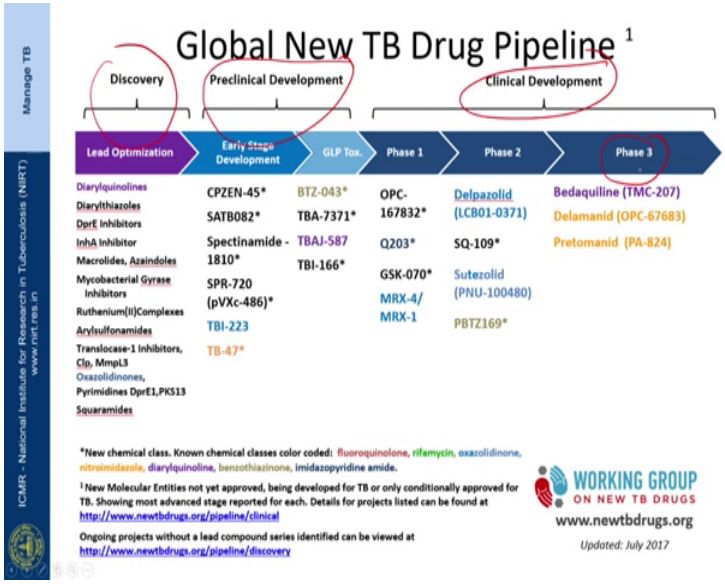

Currently there are a number of drugs that are in the pipeline, some are in the discovery phase, some are in the preclinical development stage, some are in the clinical development stage; phase 1, phase 2 and phase 3.

If you look at the newer drugs bedaquiline and delamanid and pretemanid they are in phase 3 trials and they may be available shortly for our regular use.

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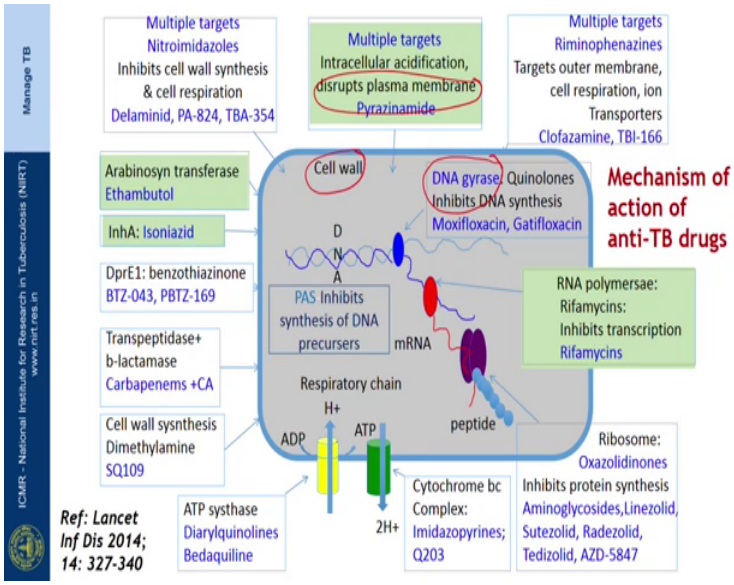

Now, this figure clearly explains the mechanism of action of the anti-TB drugs look at the isoniazid and ethambutol; they prevent the formation of the cell wall. Look at the

pyrazinamide; it disrupts the plasma membrane formation. If you take quinolones they act the DNA gyrase level inhabiting the necessary synthesis. If you take the rifampicin it acts through RNA polymerase inhibits transcription. The other drug bedaquiline a newer drug acts at the ATP synthase level.

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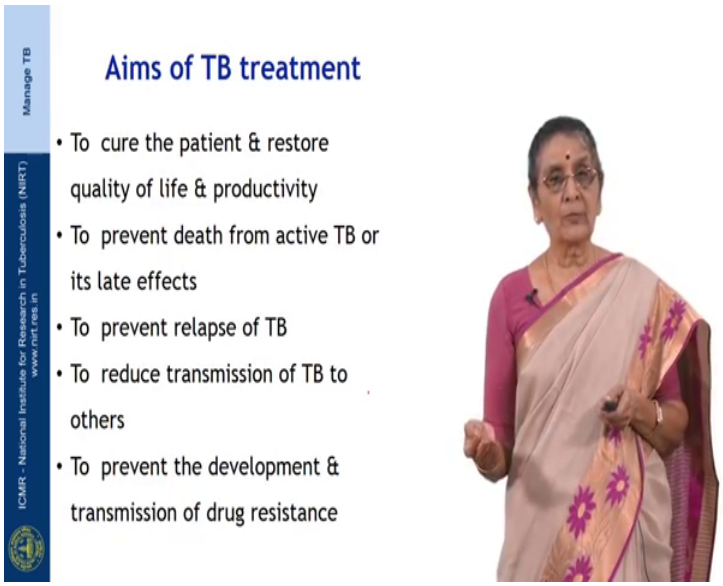

Now we come to aims of TB treatment; the main aim is to cure the patient and restore the quality of life and productivity, also to bring down mortality and also to bring down the morbidity basically of tuberculosis; from the patients point of view it is also important to prevent relapse of tuberculosis. So, from the patients point of view cure and then restore quality of life, prevent death and prevent relapses these 4 are the most important aims.

Now, from the community point of view aims are a bit slightly different, we have to aim in reducing the transmission of TB to others by giving bactericidal drugs and killing the rapid kill achieving rapid kill of bacteria, making the patients smear and culture negative. Also we have to look at the transmission of drug resistance, development of drug resistance from the community point of view; this is also achieved by rapid kill of the organisms by giving short course chemotherapy drugs of rifampicin INH pyrazinamide.

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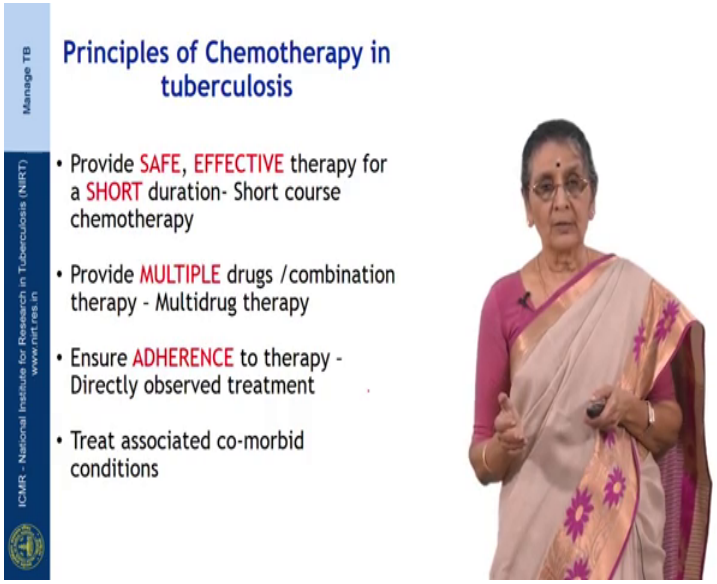

Now, let us go into the principles of chemotherapy in tuberculosis; first aim is safety and efficacy, any drug that is prescribed or any regimen that is prescribed to a patient should be safe for the patient and it also should be effective. Now, prior to start of treatment please look at the liver function and renal functions ensure they have a proper functioning liver and kidney.

This is important then you start the chemotherapy I say totally earlier drugs consisting of reforms in INH ethambutol pyrazinamide short course chemotherapy. The other principle is to use multiple drugs, combination of drugs; now why are we using multiple drugs we will come to that in the next slide. Never give a single drug, single drug will always lead to failure and resistance always your aim is to give combination of drugs.

Now, it is not only enough to give drugs, it is also important to ensure treatment regularity and adherence and help the patient to complete this treatment and WHO recommends directly observed treatment or dots in this regard. A community provider or a somebody from the patients house or a health worker helps a patient in completing the treatment. It is also equally important to look for associated co morbidity like HIV and diabetes and treat them accordingly.

So, to summarize safety efficacy is very important, use multiple drug combination that is also very important and see that the patient completes this treatment and help him by giving dots.

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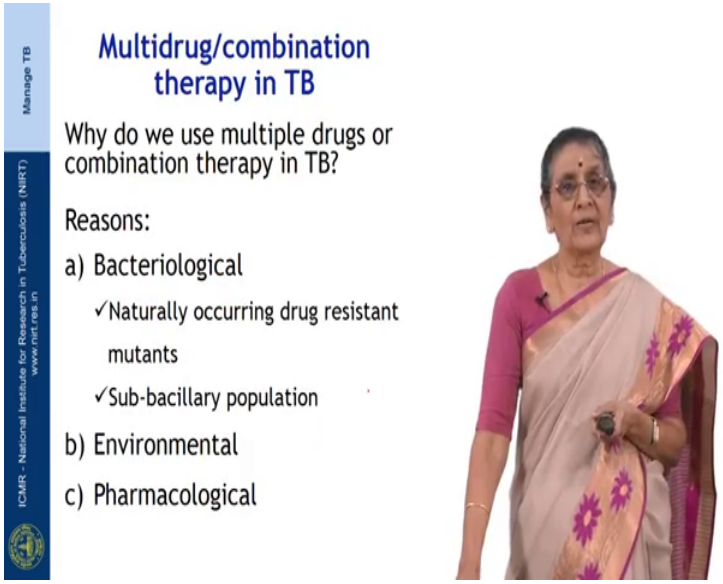

Now, why did we give a multiple drug or combination of drugs in tuberculosis? There are a number of reasons ranging from bacteriological reasons, environmental reasons and pharmacological reasons. The most important is bacteriological where you find naturally occurring drug resistant mutants that has to be attacked and also the subgroup of populations, bacillary populations with different metabolic activity we will see these 2 in later slides.

These are very important in designing regiment. Environmental and pharmacological is also equally important; environmental is it depend the drugs penetration depends upon so many factors it may be the membrane or it may be the blood brain barrier and accordingly her to prescribe drugs.

The third reason it is also equally important is the pharmacological reason; where the patient is given all the drugs together as a single dose to ensure peak serum activity which is usually above the MIC of the bacteria which ensures killing of the bacteria.

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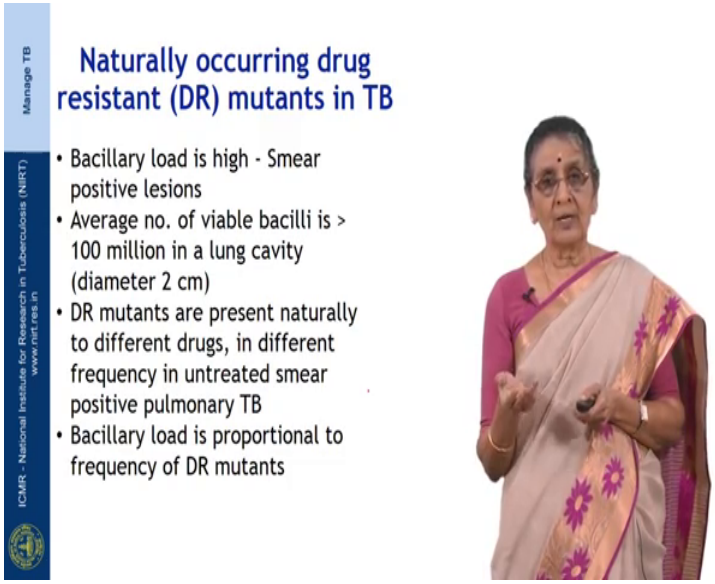

Now what are naturally occurring drug resistant mutants in TB? If you see cavitatory tuberculosis, the cavity will be teeming with bacteria and it will be millions; when you have millions of bacteria viable bacteria there are a few that may develop resistant through any one of the anti-TB drugs; which are called naturally occurring drug resistant mutants in tuberculosis.

So, this is seen whenever the bacillary load is very high especially in smear positive pulmonary TB lesions. They are mutants as I told you earlier are present naturally to different drugs and in difference frequency in an untreated smear positive pulmonary tuberculosis patient; more the number of bacteria more than they are mutants.

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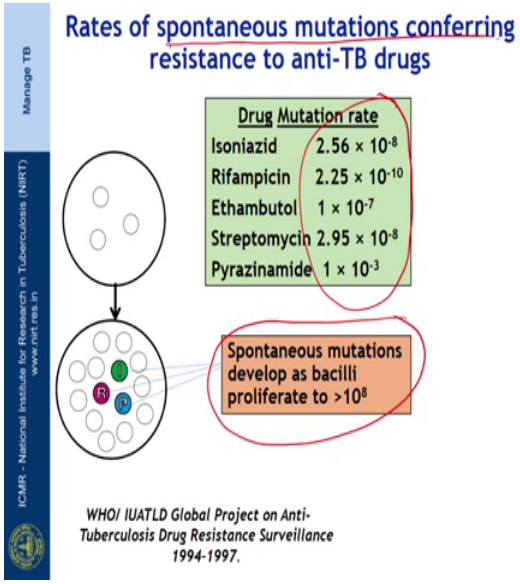

Now, this figure clearly tells you the rates of spontaneous mutations conferring resistance to anti TB drugs; if you look at isoniazid, if you look at rsifampicin ethambutol, the drug mutation rates are different for different drugs, but as you as was mentioned earlier spontaneous mutation developed whenever the bacterial count is very high more than 10 to the power of 8.

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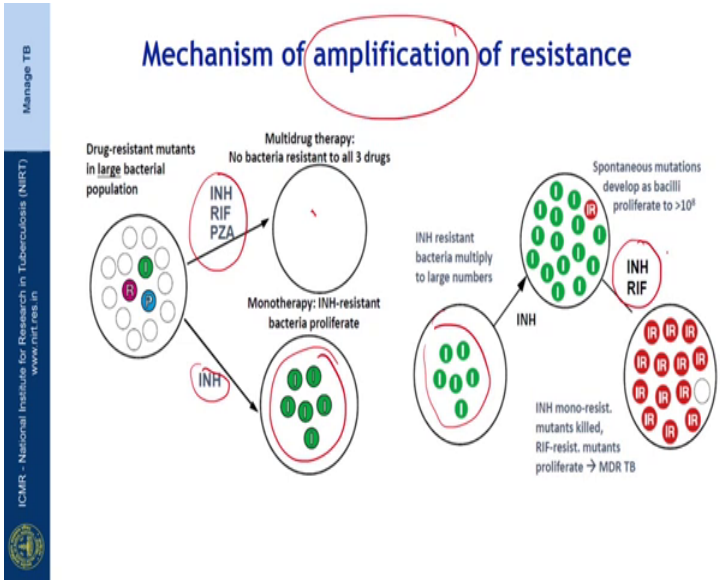

Now, this figure clearly explains the mechanism of amplification of resistance. The previous slide we saw the spontaneous mutations conferring resistance to anti TB drugs, now in this slide we will be looking at the amplification of resistance to the drugs.

If you look at this picture; whenever only INH is used if the patient harbors INH resistant organisms the this mono therapy amplified the resistance and you find more of INH resistance organisms whereas, when you treat them with 3 drugs namely INH, rifampacin and pyrazinamide all the 3 are affected and ultimately with multi drug therapy no bacterial resistance is seen to all the 3 drugs after the end of treatment.

If you look at here already you are starting with INH resistant patient you are treating only with INH, INH resistant bacteria multiply in larger numbers when you treat this patient with true drugs namely INH and rifampicin this place a way of our development of rifampicin resistance as well. So, the net result would be you have a patient with multi drug resistant TB when you use only a single drug or two drugs.

So, the principle would be to prevent the amplification of resistance use more than 2 bactericidal drugs use at least minimum 4 drugs in the earlier phase.

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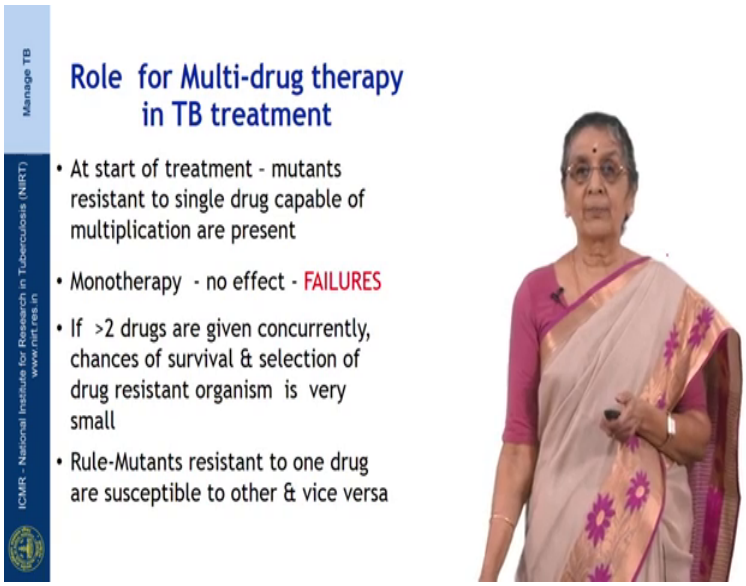

Now, let us look at the role of the multi drug therapy in TB treatment the start of the treatment mutants resistant to single drug capable of multiplication are present, if you give mono therapy it will lead to failure and more of resistance will be seen. So, if you

give 2 drugs concurrently chances of survival and selection of drug resistant organisms are very very small. The rule is mutants resistant 1 drug are susceptible to other drugs and vice versa; you use this principle in the treatment of tuberculosis, there you give multi drugs more than 4 drugs to bactericidal drugs at least in that combination to attack to achieve a kill of all the bacteria in the start of treatment.

Thank you.