Manage TB
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Lecture – 54
Newer Anti-TB drugs and regimens Session 1

Hello I am Dr. Padmapriya and I would like to discuss a Newer Anti -TB drugs and regimens in the next 2 sessions.

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What is the need for new TB drugs? Current anti TB therapy for drug sensitive TB varies for 6 to 8 months of treatment and for drug resistant TB it is for 18 to 24 months and it consists of daily regimen for drug resistant TB patients. Now, is there a need for shorter duration of treatment?

Now, shorter regimens will not only reduce the burden of treatment for patients as well as the healthcare system. It will also help us reach the target for directly observed therapy and thus increase the global coverage. There will be higher treatment completion rate as well as cure rate, and thus improving the TB control and reducing the drug resistance especially in the era of HIV epidemic.

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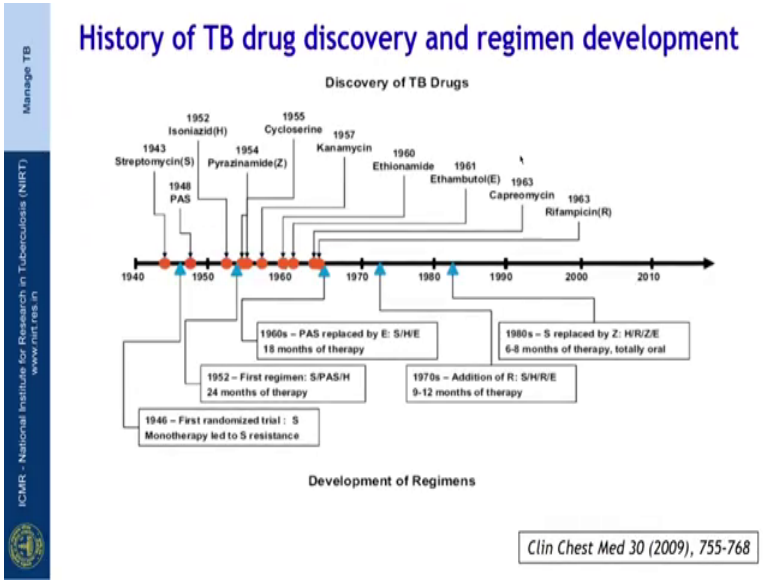

Now, if you look at the slide the history of TB drug discovery has originated way back in 1940. And over the period of years till 1960 there has been a a group of drugs discovered and brought into use.

Now, after 1960 till 2010 we do not find any orange dots the orange dots denotes the time period when new drugs been discovered. So, there has been a paucity of new drug discovery in the last 40 years, 40 to 50 years.

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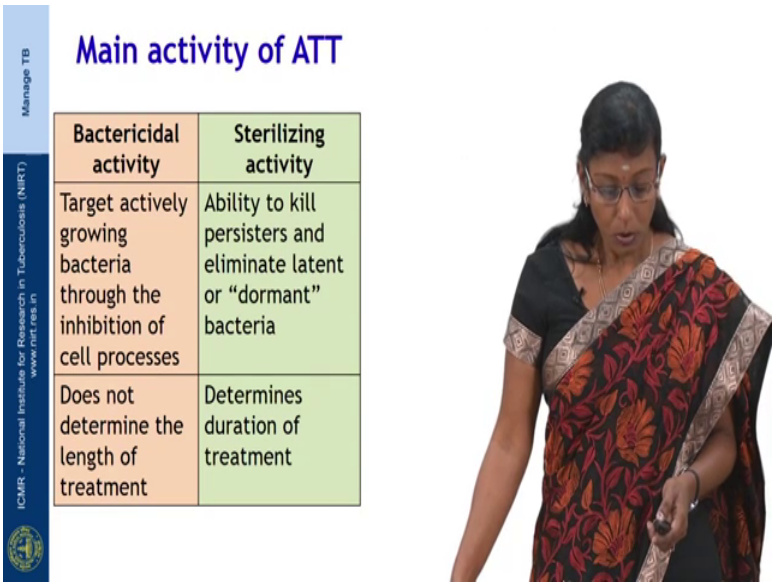

Now, the main activity of antituberculosis treatment is bimodal one it is a bactericidal activity, other one being the sterilizing activity. The bactericidal activity mainly targets the actively growing bacteria by inhibiting the cell process, now this does not determine the length or duration of treatment.

While the sterilizing activity which is the ability of the drug to kill the persistent or eliminate the latent bacilli, or the dormant bacteria. This determines the duration or the length of the treatment for antituberculosis therapy.

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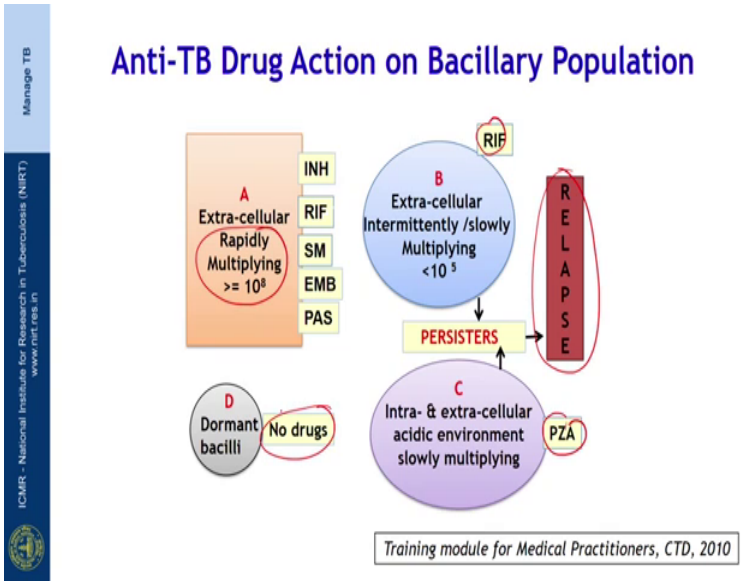

As we know the anti TB drug action basically acts on 2 types of bacteria, one the rapidly multiplying other one the persister or the slowly multiplying organisms. All the first line drugs isoniazid, rifampicin, streptomycin, ethambutol, and pas they act on the rapidly multiplying bacteria in the extracellular phase.

The rifampicin, and pyrazinamide these two drugs will act on the slowly multiplying organisms or the persisters. These persisters are responsible for the development of relapse among treated tuberculosis patient. Unfortunately we do not have any drugs as of today that acts upon the dormant bacilli.

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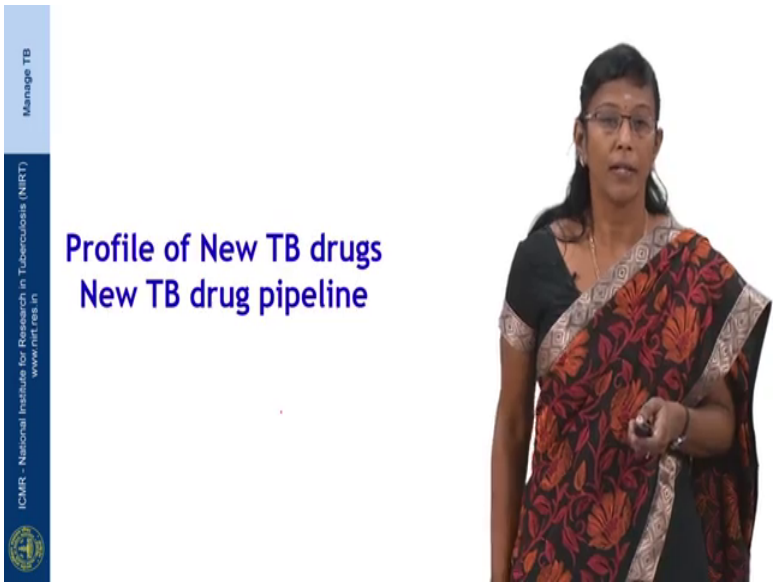

So, what are the profile of any drug that claims to have an anti TB activity?

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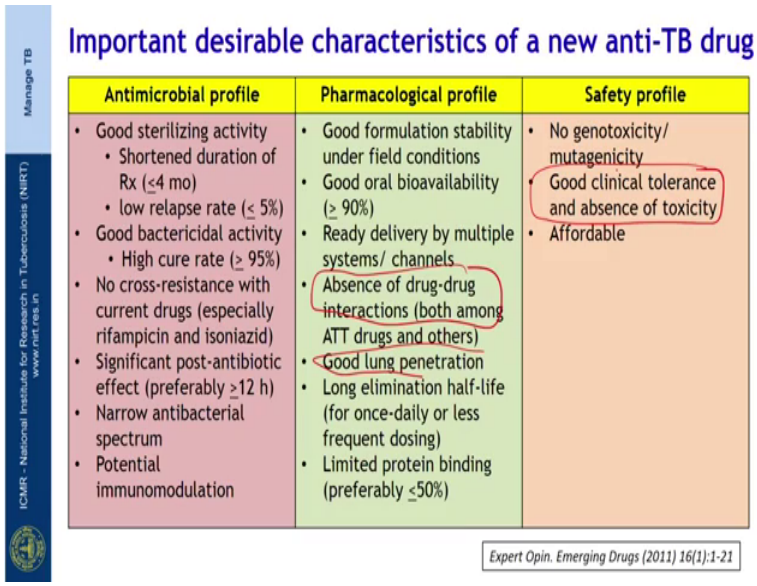

So, there are certain desirable characteristic given up for anti TB drug which includes antimicrobial profile, pharmacological profile, and the safety profile. Antimicrobial profile looks at a sterilizing activity, the bactericidal activity the presence, or absence of cross assistance with other drugs.

The drug should also have good formulation and stability in the field conditions, it should also have a good oral bioavailability and easily deliverable by multiple systems.

Most important these drug should also have no drug interactions when given along with other drugs, these drugs claiming to have anti TB activity should have good lung penetrations and long elimination half life. We are also looking at the safety profile of these drugs including good clinical tolerance, absence of toxicity, at the same time affordable at a low cost.

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Now, approach to new anti TB drug development can be threefold; one we can repurpose already existing old drugs or reengineer existing antibacterial compounds and look for the presence of the profile that we saw in the previous slide. For example, like drugs like the delamanid PA 824, the third one is a discovery of newer compounds.

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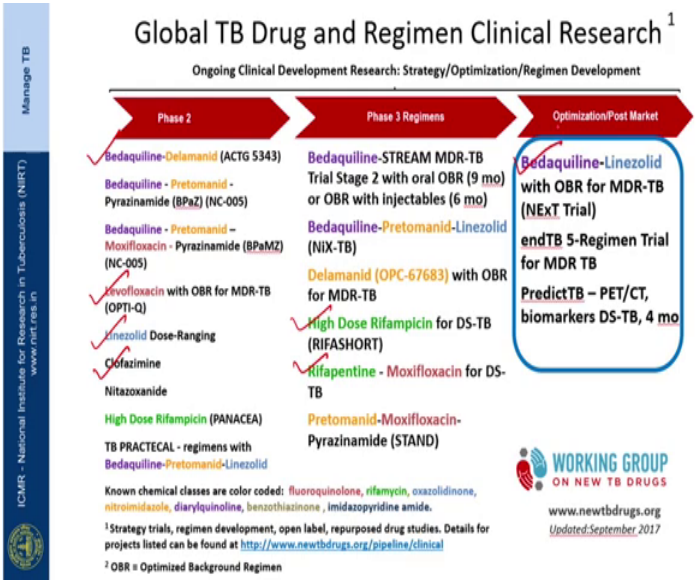

The global TB drug pipeline various drugs were tried in the la in the last many years for the last 40 to 50 years. Few of the drugs have been shortlisted and they have entered the phase 2, and phase 3 of clinical trials. Most important drugs that have entered the phase 2, phase 3 clinical trials include bedaquiline and delamanid. Various types of fluoroquinolones namely levofloxacin and moxiflox, repurpose drugs include linezolid and clofazimine.

Now, high dose rifampicin and rifapentine have also entered the phase three clinical trial for using in drug sensitive as well as drug resistant TB; Combination of drugs like bedaquiline and linezolid have also entered various phases of clinical trials to look for the ephicacy in drug resistant TB.

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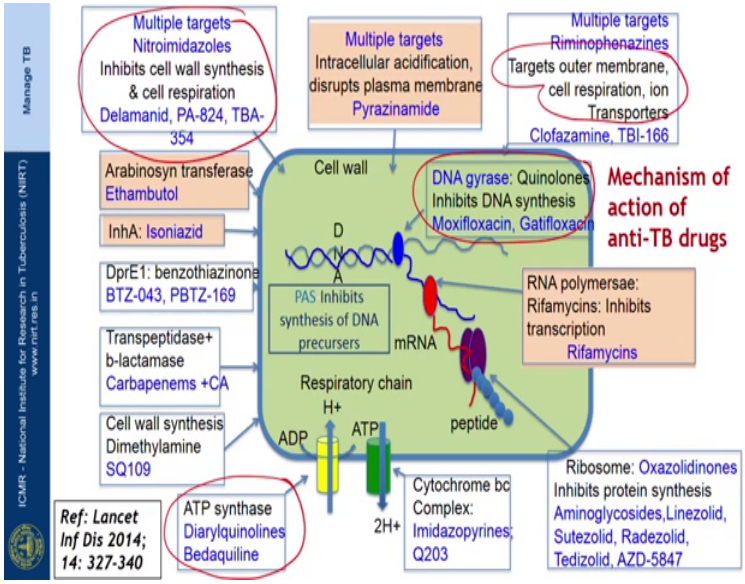

The mechanism of a newer drugs the slide here shows the mechanism of action all drugs but I would like to concentrate on mechanism of newer anti TB drugs. For example, the delamanid PA 824 they inhibit a cell wall synthesis and in turn cell respiration. The newer drug bedaquiline inhibits the ATP synthase.

Now, this is something new mode of action that is coming into the pipeline, also have the fluoroquinolones which acts for inhibiting the DNA synthesis. We also have other drugs which are either in phase 1, or phase 2 clinical trial looking at the targeting outer membrane of and the cell respiration of the mycobacterium.

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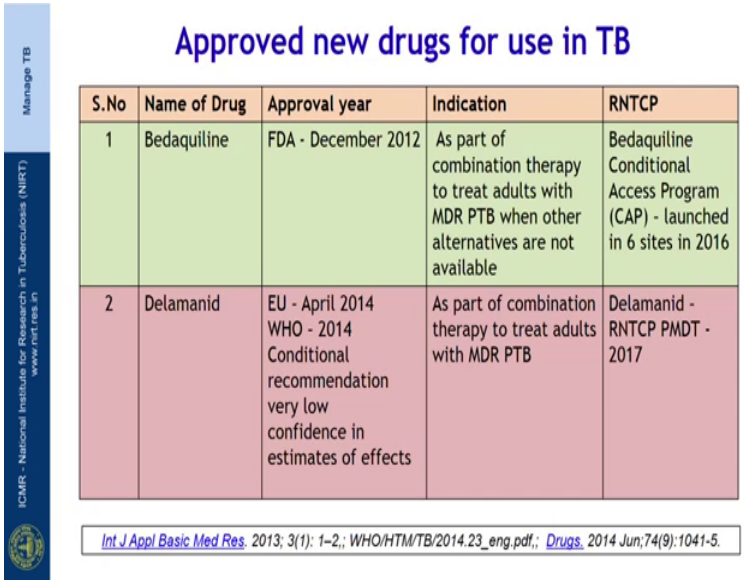

Of all the drugs that I showed you in the previous slides 3 or 4 drugs have entered into the market and have been given accelerated approval to be used in programs in the national programs, two such drug are bedaquiline, and delamanid. Bedaquiline has been recommended to be used as part of combination therapy to treat adults with MDR pulmonary TB, when there is no other alternative available.

Delamanid again has been recommended by WHO as well as European, union as part of combination therapy to treat adults with multidrug resistant pulmonary TB. Both these drugs have been introduced into the into our national TB control program as well as PMDT, as of 2016 and 2017 respectively.

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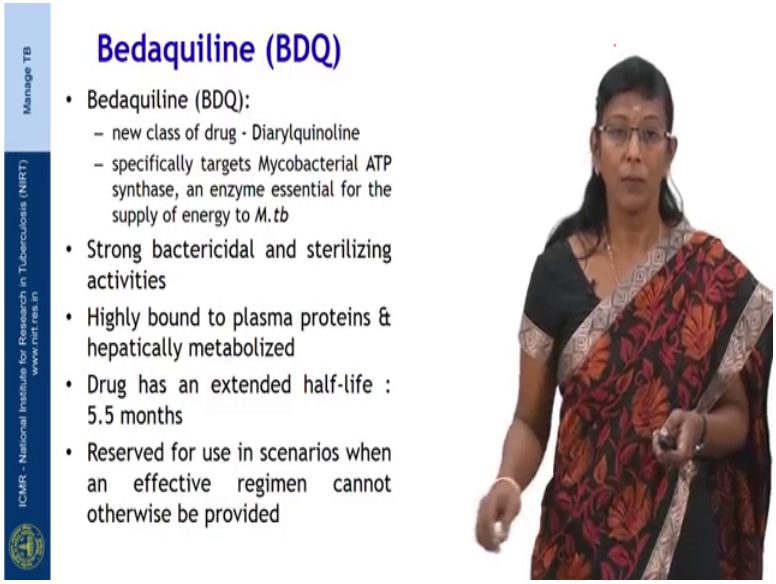

If we look at bedaquiline the newer anti TB drug this belongs to new class of drug called diarylquinoline. It specifically targets a mycobacterial ATP synthase, and enzyme essential for the supply the energy to MTB. This drug has both bactericidal as well as sterilizing activity this is highly bound to plasma protein and hepatically metabolized.

Drug has an extended half life of five and a half months it is reserved for use it scenarios for an effective regimen cannot be otherwise made to treat a multidrug resistant Tuberculosis.

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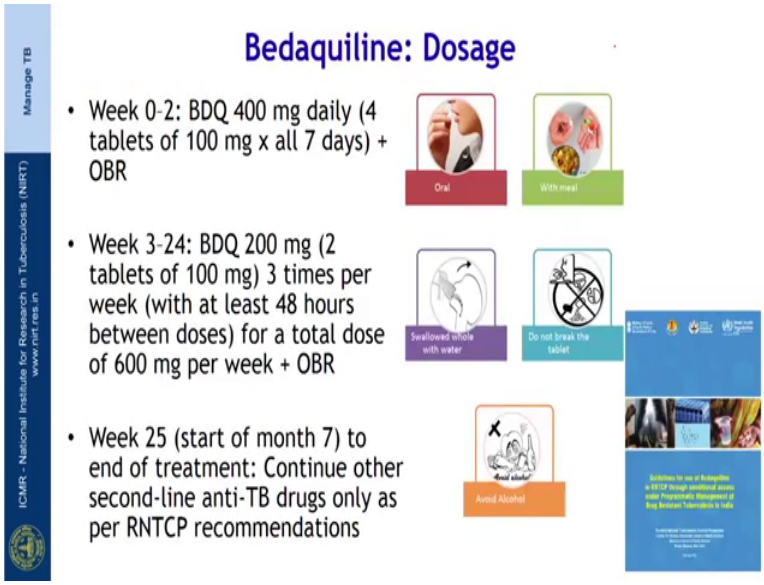

Bedaquiline is available as 100 milligram tablets it is recommended in the dose of 400 milligrams daily for the first 2 weeks. It is given us 4 tablets of 100 milligram all 7 days along with the optimized background regimen. Subsequently from week 3 to week 24 bedaquiline 200 milligram is given as 2 tablets of 100 milligram, 3 times per week at least 48 hours apart between the doses, for a total dose of 600 milligram per week along with optimized background regimen.

At the end of week 24 bedaquiline stopped from week 25th onwards continue rest of the drugs of second line anti TB drug as per the RNTCP recommendation. Bedaquiline is available as oral tablets it has to be taken immediately after food consumption, it is swallowed whole and it is not advisable to break the tablets into two. RNTCP PMDT has come out with guidelines for the use of bedaquiline through conditional access program in the management of drug resistant TB in the country.

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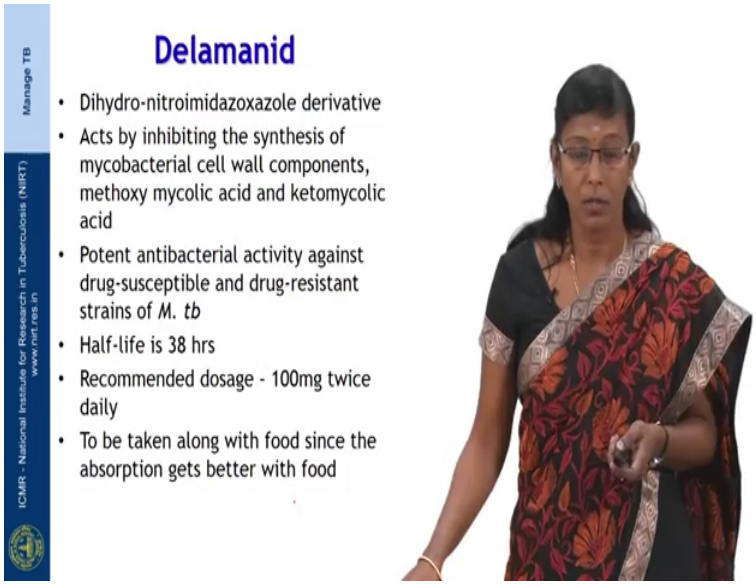

The second drug is delamanid delamanid belongs to the nitroimidazole group of drugs. It acts for inhibiting the synthesis of mycobacterial cell wall, the methoxy mycolic acid and the ketomycolic acid. It again is a potent antibacterial drug it acts against both drug acceptable as well as drug resistant strains of M TB. Unlike bedaquiline, its half life is only for 38 hours.

The recommended dosing is 100 milligram twice daily. This drug has to be taken along with food since absorption of the drug is better with food intake.

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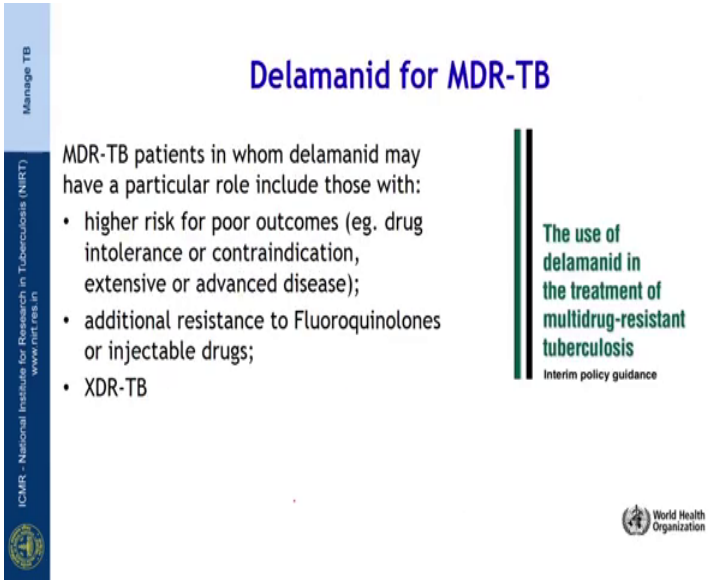

WHO has come up with a guideline for the use of delamanid in the treatment of multidrug resistant TB, especially individuals with higher risk for poor outcome like drug intolerant or extensively advanced case of drug resistant TB.

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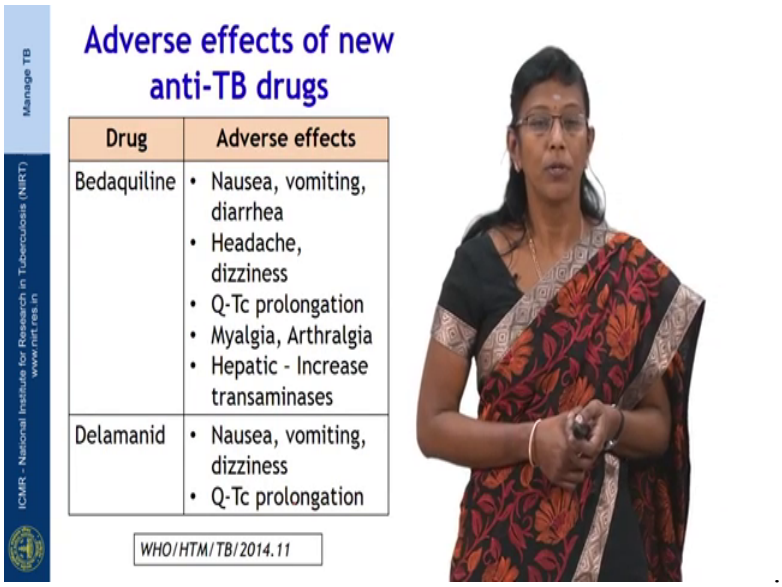

Both bedaquiline and delamanid have class adverse effect. Basically they cause of course, nausea vomiting like the other antituberculosis drugs has been used for drug resistant TB. Most important adverse event here is Q-Tc prolongation, both of them have

an cardiac effect and Q-Tc prolongation to be watched for when a individual is on either bedaquiline or delamanid.

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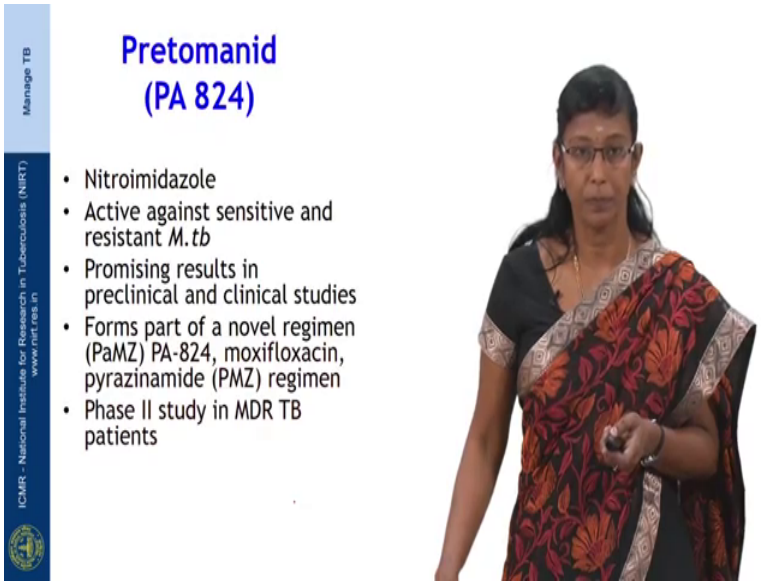

The third newer drug is protom pretomanid, now this also bigger belongs to nitroimidazole group. It is active against both drug sensitive as well as drug resistant tuberculosis, it has shown a promising results both in preclinical as well as clinical studies; Moving on from individual newer drugs to drug regimen.

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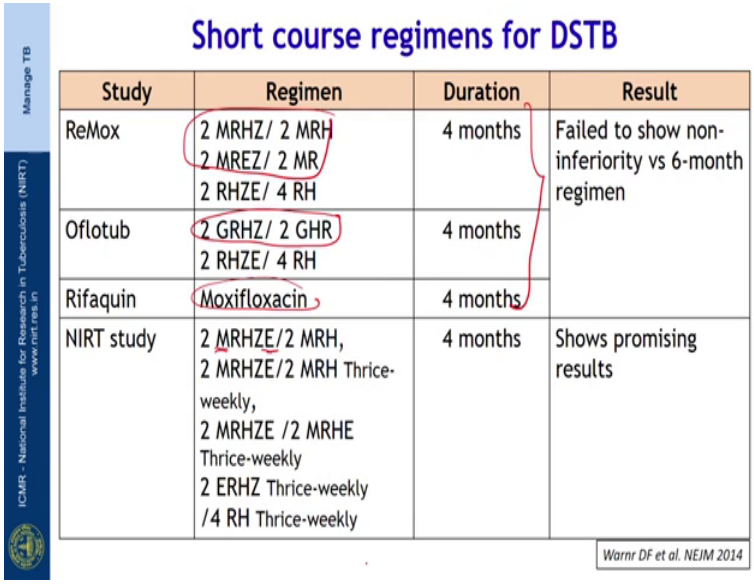

So, there are 4 new studies which is looked at the combination of fluoroquinolones along with rifa rifampicin, isoniazid, and pyrazinamide for a period of 4 months, remox oflotub and rifaquin studies where ethambutol was replaced with moxifloxacin or gatifloxacin for a period of 4 months.

In remox ethambutol has been replaced with moxifloxacin, and oflotub gatifloxacin replaces ethambutol. Rifaquin is another study where moxifloxacin also was used. All the studies have failed to show success rate beyond 6 month of regimen.

Unlike the three studies published NIRT has done a study where they have replaced moxi where they have added moxifloxacin, along with ethambutol for a period of 4 months. It was used both daily as well as in thrice weekly regimen patients were followed up for a period of 24 months and this result, has this study has shown promising results.

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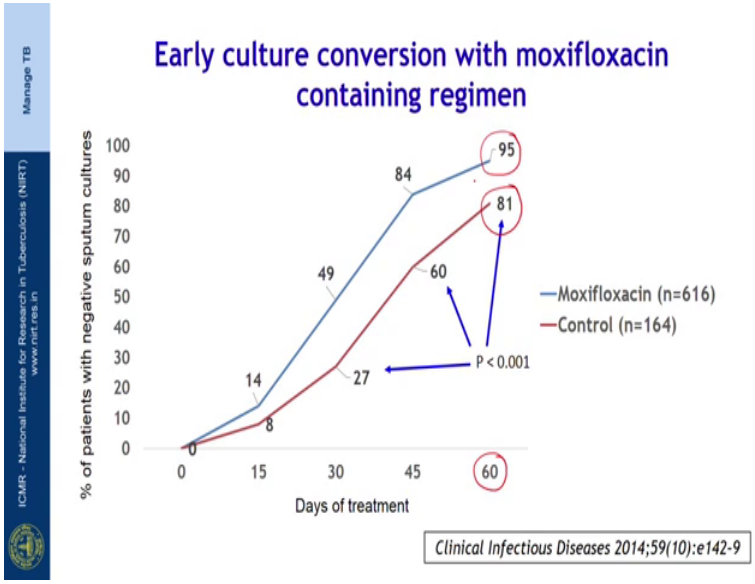

The early culture conversion was seen with moxifloxacin containing regimen. This graph here shows the red line is a control regimen of 6 month duration, the blue line is the moxifloxacin containing regimen of 4 months duration.

And you look at the culture conversion at the end of 2 months, the culture conversion with moxifloxacin containing regimen is around 95 percent as compared to 80 percent with the control regimen. We are awaiting the results of the long term results of moxifloxacin containing regimen which will be published very soon that is the end of session 1.

Thank you.