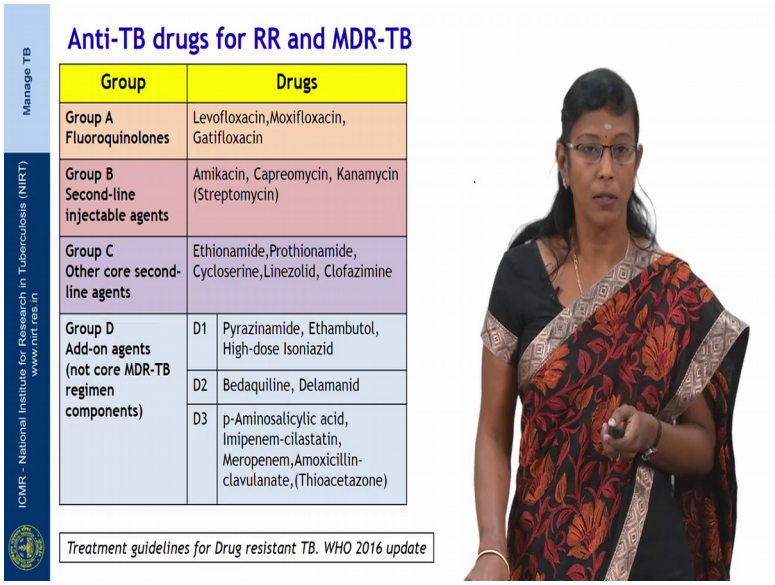
Manage TB
Dr. C. Padmapriyadarsini
National Institute for Research in Tuberculosis

Lecture – 55
Newer Anti-TB drugs and regimens Session 2

Hello I am Dr. Padmapriya and I continue with Session 2 on Newer Anti-TB drugs and regimen.

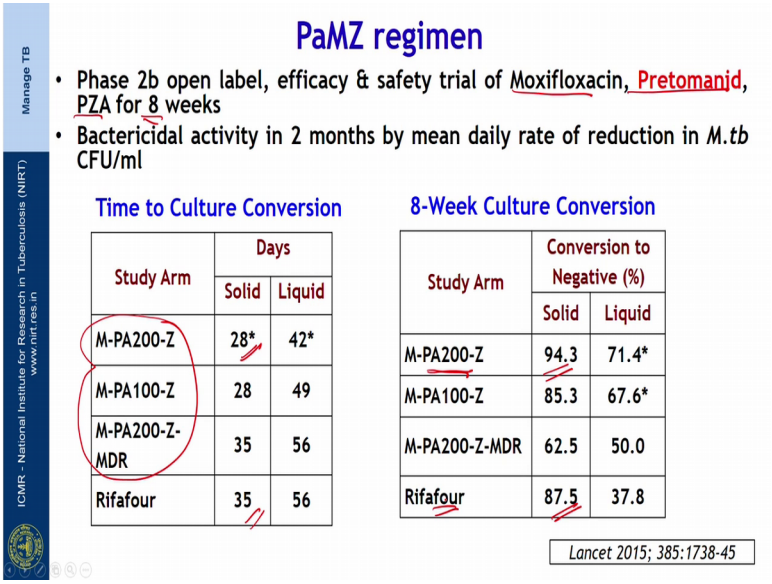
(Refer Slide Time: 00:16)



Anti-TB drug for drug resistant or MDR TB has been reclassified or regrouped into group A, group B, group C and group D. Group A consists mainly of fluoroqulnolones, levo, moxi and gatifloxacin. Group B consists of second line injectable drugs amikacin, capreomycin, kanamycin along with streptomycin.

Group C or the other second second line core agents which includes ethionamide, prothionamide, cycloserine, linezolid and clofazimine. The group D or the other add on drugs pyrazinamide, ethambutol and high dose isoniazid, the newer drug bedaquiline and delamanid and the D 3 class of drugs including pass imipenem and amoxiclap.

(Refer Slide Time: 00:59)

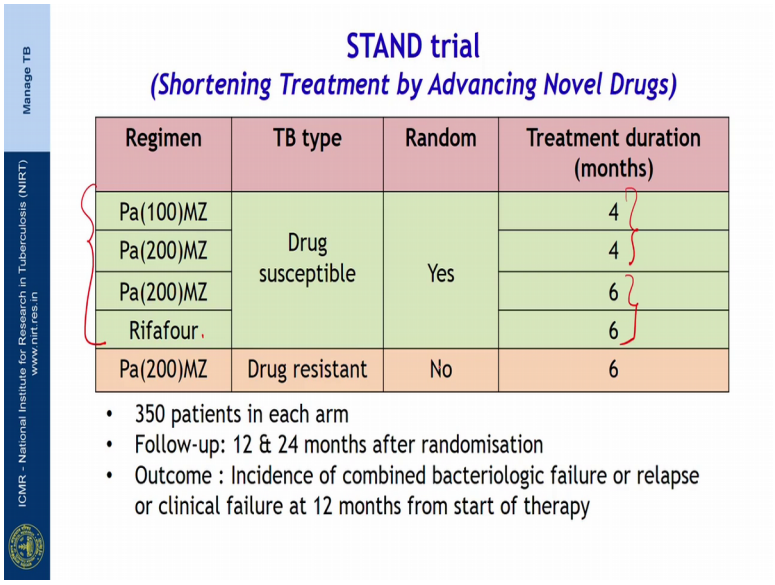


In the next few slides I want to describe the various trial regimens which have use a combination of newer drugs. The first one is a PaMZ regimen, this is a phase 2b open label, efficacy and safety trial that is combined moxifloxacin, pretomanid and pyrazinamide for a period of 8 weeks. They have tried to look at the bactericidal activity of this particular regimen and they have seen the reduction the colony count of M tuberculosis.

Now, if you look at these table the study arm which contained this particular combination of PaMZ has shown a reduction or time to culture conversion is much faster or much earlier than the regimen which should not contain the newer drug pretomanid. It is around 28 days in the solid culture as compared to 35 days in the control regimen.

The 8 week culture conversion again was around if you look at the proportion of patients assured culture conversion at the end of 8 weeks of treatment. Around 94 percent was seen in the regimen containing 200 milligrams of pretomanid as compared to 88 percent in the control arm.

(Refer Slide Time: 02:12)

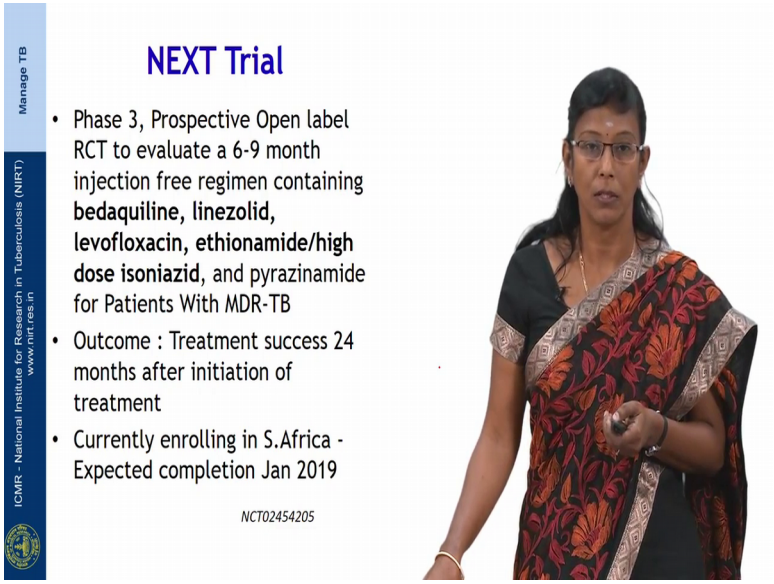


Now, based on these earlier findings of culture conversion 8 weeks, the group went on to do a control clinical trial among 350 patients and look see whether they can shorten the treatment duration to 4 months instead of 6 months. They have got two different arms, the one group is all drug sensitive TB where they comparing the pretomanid of 100 milligrams versus 200 milligram in drug sensitive patients as compared to the control regimen of rifafour.

Now, these regimen is given for a period of 4 months versus 6 months. They also have an observational arm where a they are giving 200 milligram of pretomanid along with moxifloxacin and pyrazinamide in drug resistant TB.

This is an observational cohort observational group and the treatment is going to be given for 6 months and see the response at the end of 12 months and 24 months. They are looking at outcome of instance of combined bacteriologic failure or relapse or clinical failure at the end of 12 months from start of therapy.

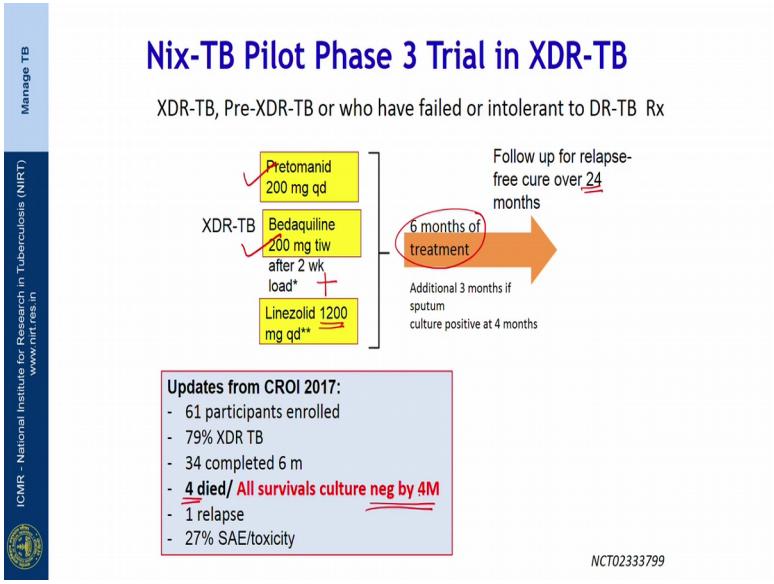
(Refer Slide Time: 03:08)



The next trial is the next trial. Next trial is nothing, but a phase 3 prospective open label randomised clinical trial. Looking at a combination of newer drugs bedaquiline, linezolid, levoflox and ethionamide along with pyrazinamide in drug resistant TB patients, this combination will be given for a period of 6 to 9 months. Important thing to note here there is no injectables in this regimen.

The regimen will be given for 6 months in MDR TB patients can be extended up to 9 months in case of failure of culture conversion at the end of 4 months of treatment. All the patients will be followed up for a period of 24 months after initiation of treatment to look for the treatment success in terms of failure as well as relapse. The study is currently enrolling patients and we expect the regimen the trial to get completed by 2019.

(Refer Slide Time: 03:55)

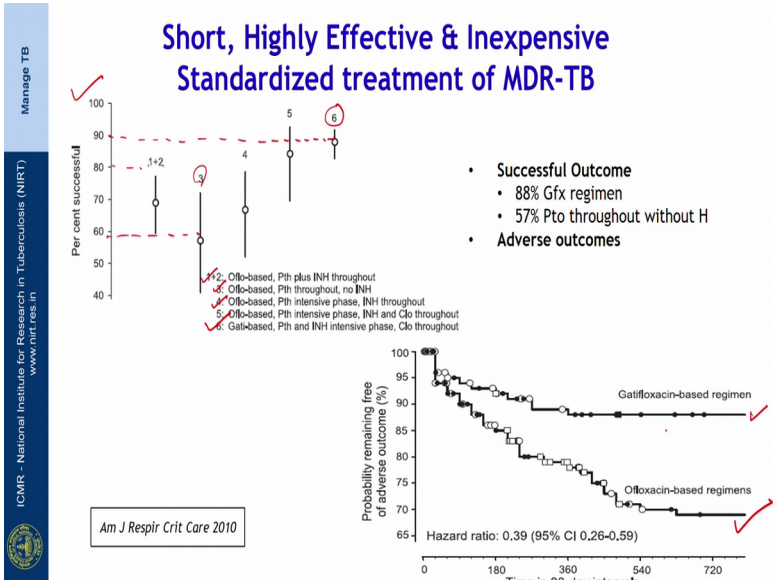


Another trial that is being tried for extensively drug resistant TB patient is by combining two new drugs. So, whatever we have seen so, far is combination of one new drug with existing drugs. Now, we have two new drugs in the regimen pretomanide 200 milligram once daily along with bedaquiline in the recommend doses after the loading dose of 400 milligram, 200 milligram to be continued thrice weekly. These two new drugs a combined with linezolid at the day dosing of 1200 milligram once a day.

Now, this is being tried out in extensively drug resistant and pre extensively drug resistant TB patient or those who have failed or are intolerant to DR TB treatment. The whole duration of treatment is for 6 months, it s a non injectable fully oral regimen. Patients will be followed up for 24 months after completion of treatment to look for the presence failure or relapse.

So, far the results that we have from next TB trial 61 participants have been enrolled, 79 percent of them happen to be XDR TB and the remaining a pre XDR patients, 34 patients have completed 6 months of treatment, among them 4 have died the remaining all have become culture negative as early as 4 months of treatment. Further results are awaited from the study.

(Refer Slide Time: 05:10)

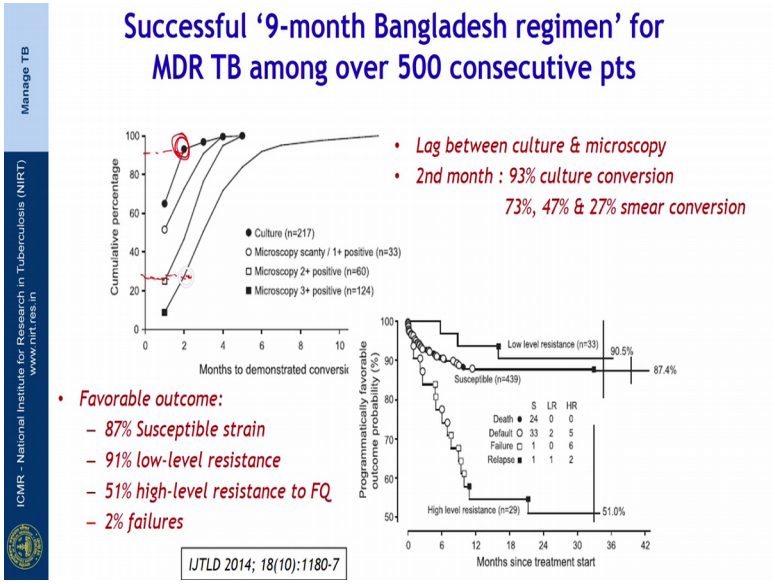


Now, moving on from those newer drugs to the drugs using fluoroqulnolones; now, this is short course regimen that is being tried in Bangladesh. Now, this graph here it shows a various regimen that was tried in the Bangladesh regimen, the first one is a ofloxacin 1 and 2 are ofloxacin based regimen along with prothionamide, isoniazid and other classes of group of drugs. Regimen 3 is ofloxacin based without isoniazid. Regimen 4 is again prothionamide INH ofloxacin based regimen.

If you look at the regimen 6, the regimen 6 they have replaced ofloxacin with gatifloxacin drug along with prothionamide unisoniazid in the intensive phase and chlofasomine added on to the regimen and continued throughout the continuation phase. Now, if you look at the success rate at the end of 6 months of treatment, the regimen that is used gatifloxacin has a treatment success rate of around 88 percent. As compared to other regimens which vary somewhere between 56 percent to 80 percent.

Now, most important thing to note here is the presence of isoniazid. If isonoazid was added to the regimen the success rate was higher as compared to regimen but it did not have isoniazid when it was given along with ofloxacin. The graph below shows the response to treatment. Now, gatifloxacin regimen had a very lower rate of adverse events as compared to ofloxacin based regimen. The hazard ratio of hazard ratio of when patient remain toxicity free or absence of toxicity was higher in a gatifloxacin based regimen as compared to a oflaxacin based regimen.

(Refer Slide Time: 06:54)

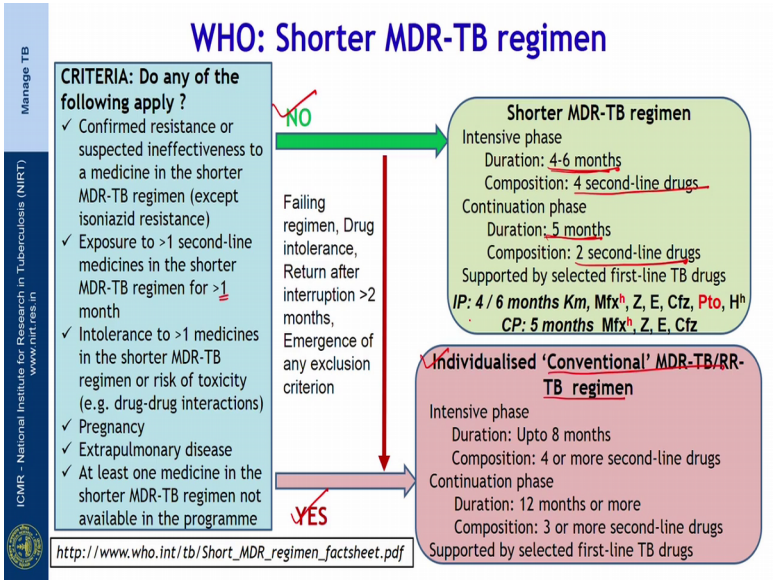


Now, looking at the success of this 9 month Bangladesh regimen; many countries wanted to adopt this regimen and there was a study that is done at a 3 or 4 countries and they replicated the same regimen in MDR TB patients in multiple countries. So, this is the result of the 9 month Bangladesh regimen among MDR TB patient in 500 MDR TB cases in multiple countries. Now if you look at this graph here this is the success rate success rate of culture.

So, the culture there is more than 80 more than 85 percent of culture conversion and if you look at this graph the third graph it is a smear status. So, the same time point the same time point when someone shows culture conversion they could have been culture smear positive.

So, what we want to say here is a lag between culture conversion and microscopic results. The second month there is 93 percent of culture conversion as compared to the smear conversion which varies anywhere from 27 percent to 73 percent. Hence, if a patient is suppose to be on a short course regimen it is mandatory that its followed up with culture conversions and not just to smear conversion alone.

(Refer Slide Time: 08:05)



Now, based on the results of the short course regimen, 500 MDR TB patients WHO recommended the use of shorter MDR TB regimen; Now, what is a criteria or who are the patients were eligible to get a shorter MDR TB regimen? Look for the presence of resistance; confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR TB regimen. Have they been exposed to more than 1 second line medicine in the shorter MDR TB regimen for more than a period of 1 month? Is a patient intolerant to more than one medicine in the shorter MDR regimen?

Presence of pregnancy, presence of extra pulmonary disease or at least one drug which is not available in the program; if the answer to any of these question is yes, the patient is not eligible for shorter MDR TB regimen and what he has to get is a individualized conventional MDR TB regimen consisting of an intensive phase and a continuation phase, the IP here is for a period of 8 months followed by continuation phase for a period of 12 months.

Now, if any of if answers to all this questions given here is a no, then the patient becomes eligible to receive a shorter MDR TB regimen. The shorter MDR TB regimen is for a period of 9 months, 4 to 6 months of intensive phase and 5 months of continuation phase. The 4 to 6 month of intensive phase will have 4 second line drugs, the 5 months of continuation phase will have 2 second line drugs. So, in short the IP will have 4 to 6 months of kanamycin, high dose moxifloxacin, pyrazinamide, ethambutol along with

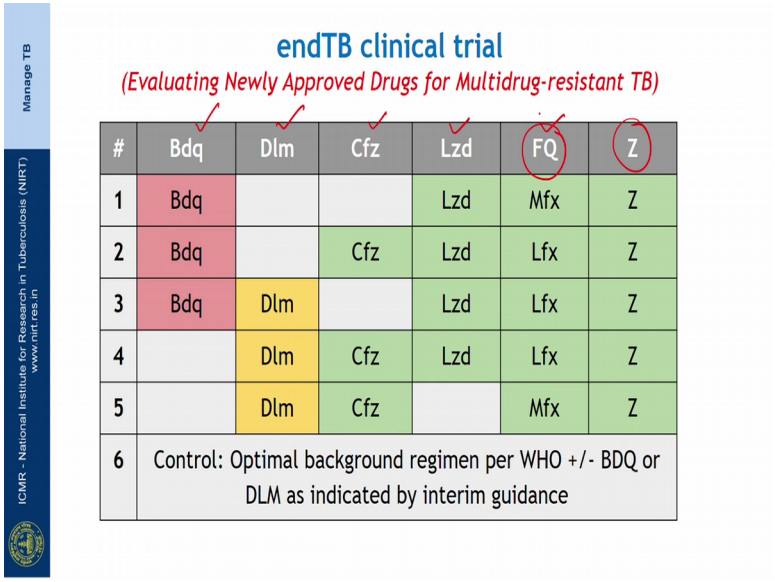
clofazimine, prothionamide and high dosage. The continuation phase they get 5 months of high dose moxifloxacin along with pyrazinamide, ethambutol and clofazimine.

(Refer Slide Time: 09:52)

The meta analysis from the shorter MDR regimen has shown about 796 patient who receive the shorter MDR regimen in 5 countries, their success rate of 83 percent against the current success rate of 30 to 50 percent with the conventional 24 month regimen.

The failure and relapse were more frequent in individuals who are treated with moxifloxacin, strains which were resistant to pyrazinamide or any of the fluoroqulnolones and absence of culture conversion by the end of 2 months of treatment.

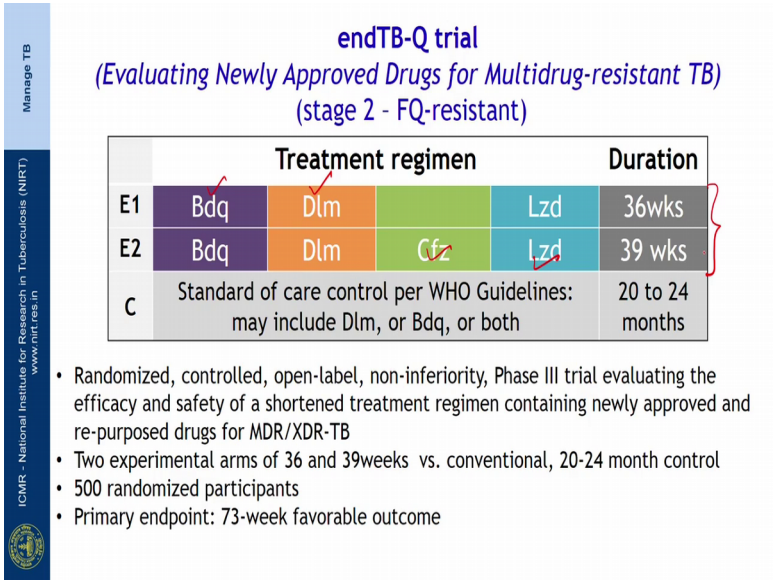
(Refer Slide Time: 10:20)



Based on the results from shorter course regimen and seeing the success of fully oral regimen few other investigators are gone on to plan other trials combining two newer drug or other repurpose drugs. One of such trial is endTB clinical trial; endTB standing for stands for evaluating newly approved drugs for multi drug resistant TB. Here this a combination of bedaquiline delamanid the two new drugs, clofazimine and linezolid these are repurpose drugs, as well as fluoroqulnolone and pyrazinamide anti bacterial drugs have being used for drug resistant TB.

They have 6 arms in various combinations. This is given compared along with individuals who will receive a control regimen. The control regimen is the WHO or the countrywide program regimen.

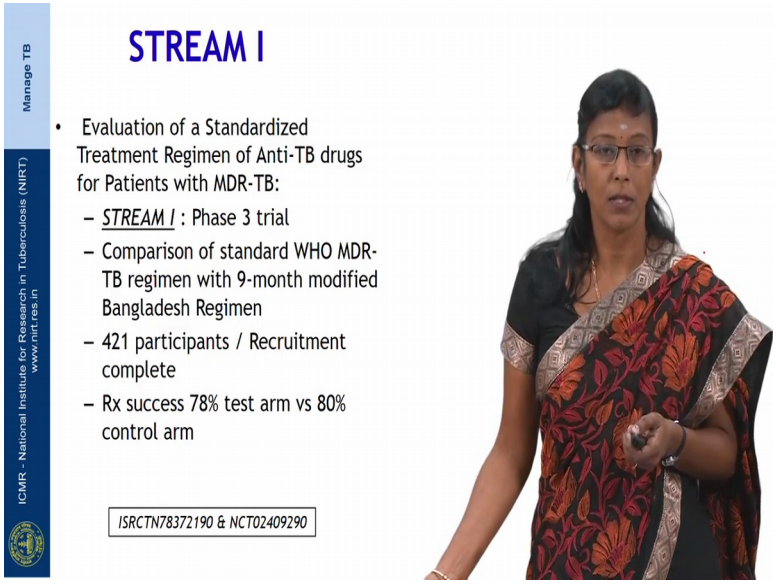
(Refer Slide Time: 11:12)



Another trial is endTB-Q trial; the endTB-Q trial is for patients who are fluoroqulnolones resistant. This has 2 arms combining bedaquiline, delamanid with clofazimine and linezolid; given for a period of 6 months to 9 months and this will be compare with the standard of care control regimen as per the WHO guidelines.

Now, many countries have been including delamanid and bedaquiline in their national programs and if any one starts on delamanid and Bdq containing WHO guidelines regimen, they will also be included in the study. So, this is there will be 500 randomized participants in this trial and the trial is yet to begin in few countries.

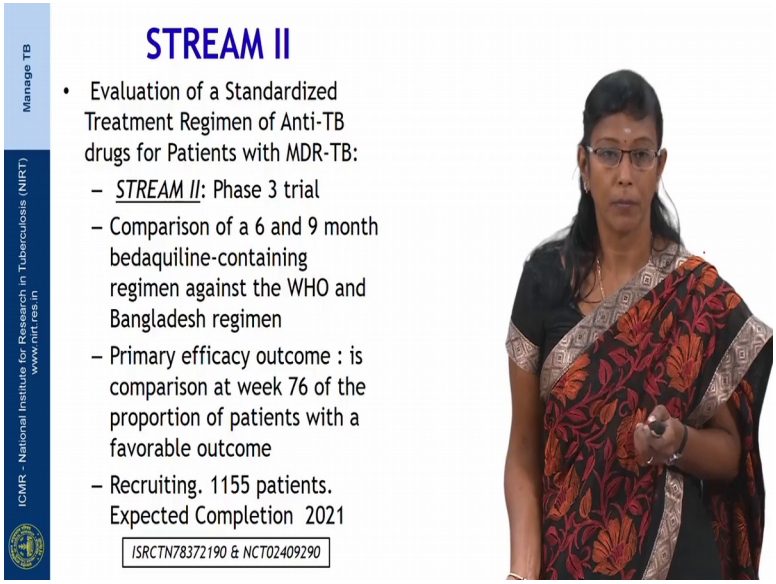
(Refer Slide Time: 11:50)



Stream 1, a stream is evaluation of standardized treatment regimen of anti TB drugs for patients with MDR TB. This is there are two phase stages to this trial. The stream 1 is a phase 3 clinical trial.

It will compare the WHO MDR TB regimen with a 9 month Bangladesh regimen with a slight modification where gatifloxacin was used for in the Bangladesh regimen it will be replaced here with moxifloxacin, 421 patient have been recruited the study, the success rate shown so, far is 78 percent in the test arm as compared to 80 percent in the control arm.

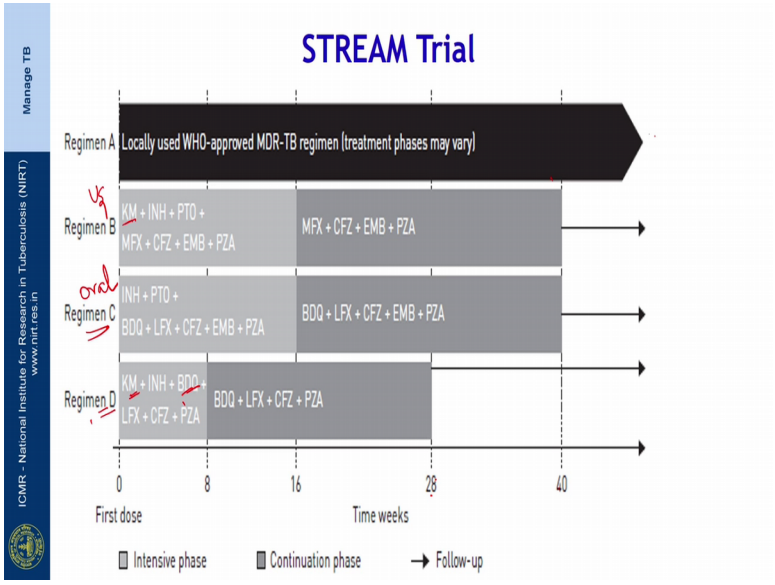
(Refer Slide Time: 12:24)



The stream 2 is a phase 3 clinical trial with a advent of bedaquiline and availability in many countries. They have added two more regimen to this trial. It will compare a 6 and 9 month bedaquiline containing regimen.

Again it is a WHO control regimen and the Bangladesh regimen. The primary outcome of this study is to look at week 76 of the proportion of patients with a favourable outcome in the multiple regimens.

(Refer Slide Time: 12:49)



So, the stream trial regimens are the regimen A is a WHO approved MDR TB regimen. This will be compared against regimen B, C and D. The regimen B will have an injectable in the regimen, it is kanamycin, isoniazid with protonamide, moxifloxacin, clofazimine, EMB and pyrazinamide. Regimen C is a fully oral non injectable regimen it has bedaquiline levofloxacin clofazimine along with INH ethambutol and pyrazinamide. Regimen 4 again has an injectable in the regimen, but it will also have bedaquiline.

So, it is kanamycin, isoniazid, bedaquiline along with levofloxacin and clofazimine. Now, most of the regimen A will be continued for the entire 24 months, regimen B will be given for a period of 40 weeks whereas, regimen D which has kanamycin as well as bedaquiline will be tried for a period of 28 weeks. All the patients will be followed up for 12 months post treatment.

(Refer Slide Time: 13:46)

Newer trial intreated by India ICMR is a beat trial, the beat trial is a non injectable all oral short course regimen for extensively drug resistant and multiple drug resistant TB patients.

This trial will look at the combination of bedaquiline, delamanid, linezolid and clofazimine, 4 drugs to be given daily for a period of 6 to 9 months. It has 2 phases with this trial in the XDR and Pre XDR TB patients the prospective cohort of 155 patients at 6 sites in the country. The MDR TB trial will have it is a phase 3, parallel arm, open label randomized clinical trial.

(Refer Slide Time: 14:24)

There are few challenges in the new drug development as well as new drug regimens. Greatest challenge is the design of the TB clinical trial, a phase 3 clinical trial has to be done at large scale with large number of patients has to be randomized and multi centric. It is not only expensive, but also challenging to do this trial in multiple sites in a uniform fashion. Efficacy evaluation requires relapse rate to be the end point.

It has to be done for a period of 1 to 2 years after treatment and these patients have to be followed up after the completion of treatment. But drug development in children it is a it is a ball game of it is own along with HIV infected individuals. There is also always the fear of drug usage or miss usage in the private sector.

So, with that we come to the end of session 2 of new anti-TB drugs and development.

Thank you.