Manage TB
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Lecture – 42
Management of Patients with HIV-TB coinfection

Welcome to session 2; dealing with HIV TB. In this session we will deal with the influence of each of the diseases, the interactions between the therapies for both diseases and how we can maximise therapy and solve the problems due to these interactions.

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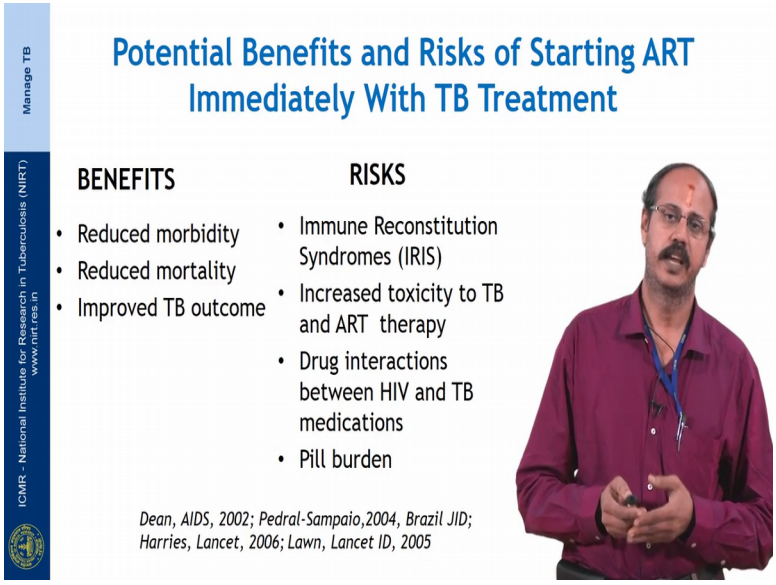

It has been resolved by various trials that ART should be started as early as possible when you diagnose HIV; thanks to the program now that with the irrespective of CD 4 you start ART immediately and TB is no exclusion even in TB you need to start ART early.

The advantages you know inevitable, that there is reduced morbidity, reduced mortality, there is improved TB outcome not only TB outcome, but any of the opportunistic infections the outcome would be better if you start ART early, but of course, there are problems, there are bottlenecks. The most important is immune reconstitution

inflammatory syndrome which is an under diagnosed, underestimated syndrome because of increase or rejuvenation of immunity; there is additive toxicity, accumulative toxicity because of both the drugs are given at the same time. Drug-drug interactions are there and of course, not to talk about pill burden which is going to be increased when you are dealing with TB and HIV.

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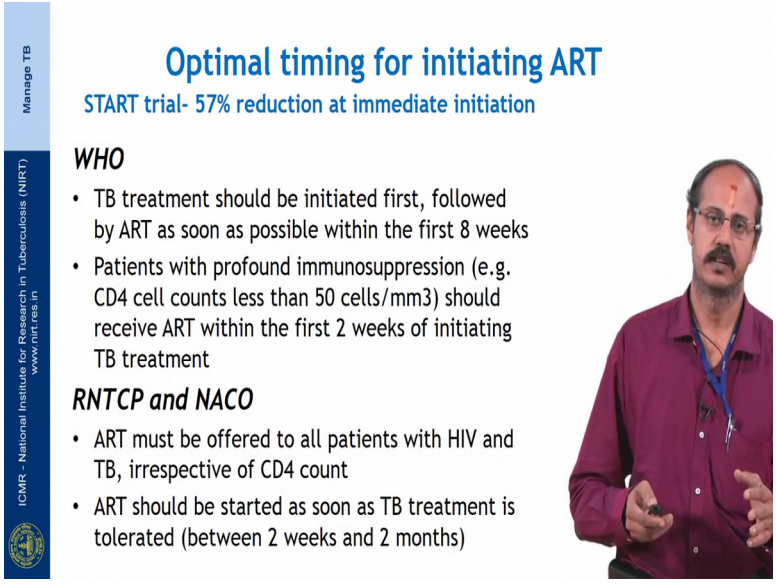

What is the optimal timing of initiating ART? The start trailer shown that; there is phenomenal reduction in mortality and morbidity if you do it immediately. The same is reflected with the WHO on the local on Indian guidelines; after TB treatment is started, we should start ART as early as possible within 8 weeks and the Indian guidelines shows that between 2 2 weeks to 2 months; that is it is quite known that we should start ART within the intensive phase.

But the caveat is what we have found with our own experiences that; when patients are having very severe immunodeficiency in the form of CD 4 less than 100 you need to start immediately.

But convincing the patient and counselling the patients about the occurrence of immune recursion inflammatory syndrome, but if the CD 4 is most than 100 you have to wait for

the patient to respond to your specific treatment as in this case it is going to be tuberculosis therapy.

Once the patient shows some improvement with ATT, you then start after the patients stabilises you then start the patient an ART then you will know what you are dealing with; whether you are dealing with iris, whether dealing toxicity or whether it is a failure or is actually something else is much more easy for us to detect if you are going to face out this regimens in this sequential way.

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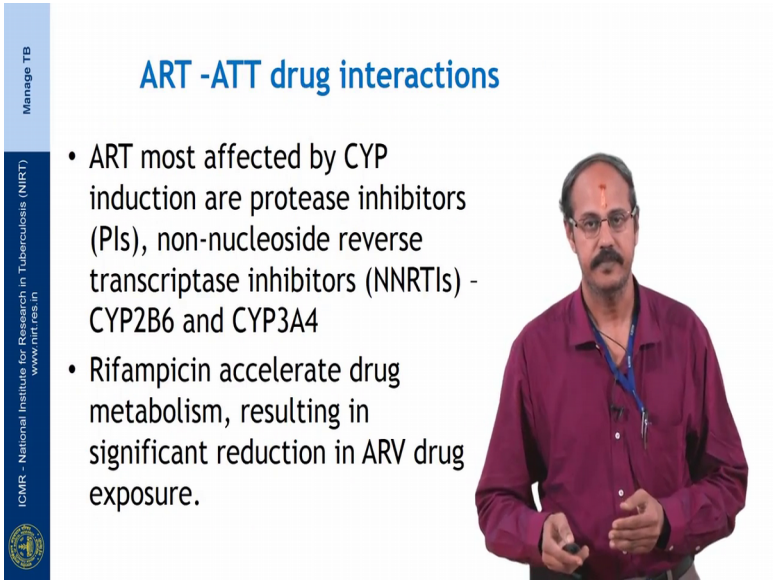

ART-ATT interactions as I told you everything involves the CYP 450 system. If the more important interactions are with protease inhibitors and non-nucleus, reverse transcriptase inhibitors with rifampicin; we have to as I told you earlier we have to go with rifabutin, rifampicin reduces the drug concentration it also reduces the concentration of FRS not that it does not interact with FRS, but is a lesser extent and hence they are palatable regimens.

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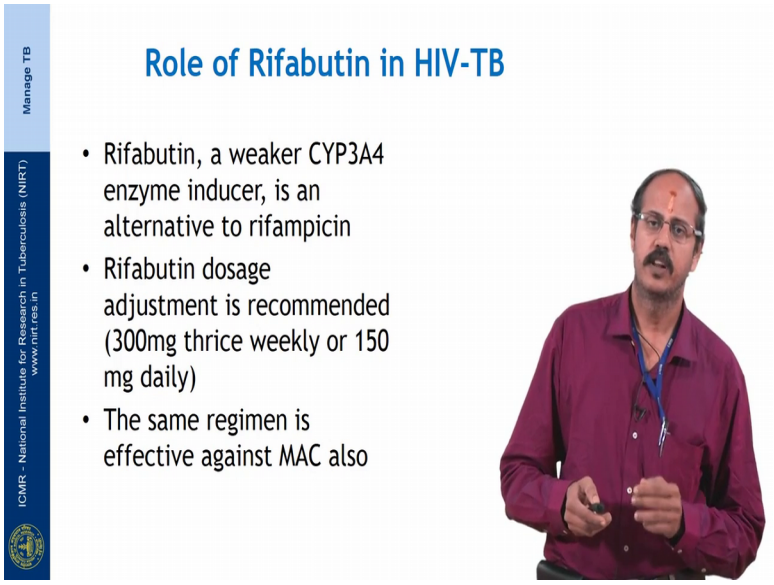

Role of rifabutin HIV TB as I told you; rifabutin is a weaker CYP 3 4 inducer and can be an effective alternative to rifampicin. The toxicity are more or less similar except for chorioretinitis and thrombocytopenia. The dosage has to be adjusted with respect to each of the PI's; the usual recommended dosages rifabutin is 150 milligram daily or 300 milligram thrice weekly, but international standards are even gone up to 300 milligrams even daily.

There is an indirect advantage of using the rifabutin most of this patients who use protease inhibiters are patients who have failed therapy to ART and they may have coexistent MAC or mycobacterium intracellular even in these cases rifabutin is much more effective a combination of rifabutin is INH and (Refer Time: 04:05) much more effective than rifampicin.

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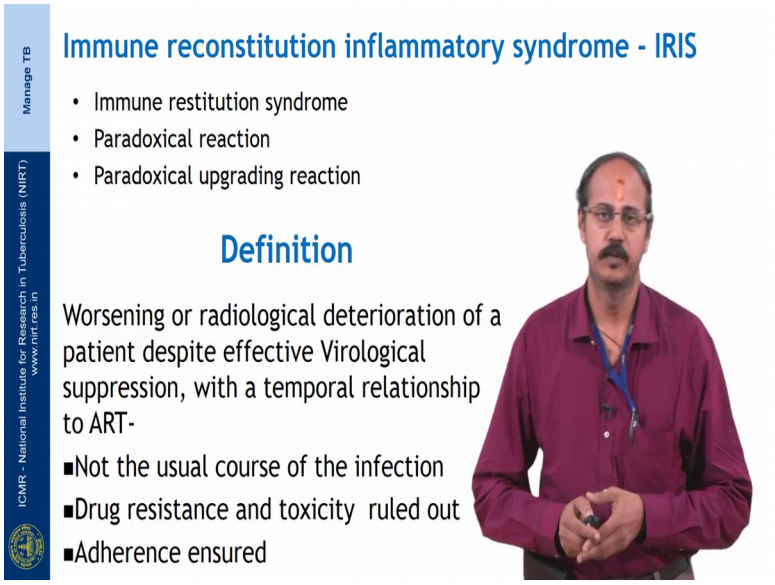

Coming to immune reconstitution inflammatory syndrome; this is an underdiagnosed underestimated syndrome. More commonly occurring with patients being start on ART very close to intensive phase of course, the program has done a lot in reducing the syndrome means asking patients to start taking ART at an early day when the CD 4 does not fall down, but once the CD 4 falls down; if you are going to start ART early you get more incidences. In fact, our studies have the highest incidences of IRIS reported to be around the range of 36 to 58 percent.

The other names of paradoxical reaction a paradoxical upgrading reaction it is nothing but worsening or radiological deterioration of a patient, with a temporal improvement with specific therapy as in this case it is TB therapy. There is effective biological suppression in the form of reduce viral load at least 0.5 to 1 law, but the patient has worsening of symptoms or there is a radiological deterioration. This cannot be explained by the usual course of infections

Three other things have to be ruled out one is non-adherence, second is drug toxicity, third and most important mimic is emergence of drug resistance.

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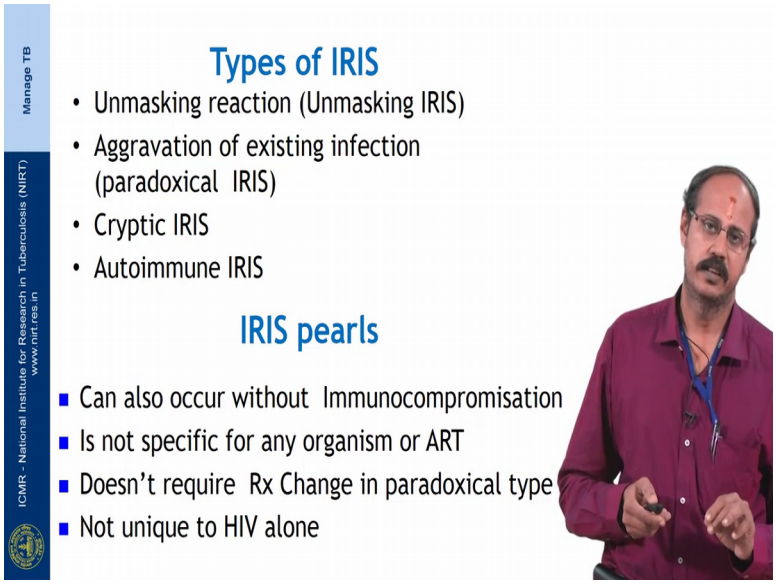

There are various types where I am going to concentrate only on paradoxical; unmasking reaction is nothing but a patient who is symptom asymptomatic in the beginning you start ART in this patient, he throws out or unmask or unveils an opportunistic infection including TB.

In a country like India is difficult to differentiate between undiagnosed TB and unmasking iris, but the solution is very simple all that you need to do is treat this patients as they do not have previous history of anti-tuberculosis treatment. Paradoxical reaction is easy to diagnose difficult to treat than unmasking reaction, you have a patients started on ATT his symptoms improve when you give ART he diterates; that is classical of paradoxical iris.

Cryptic or radiological IRIS is where the patient total asymptomatic, you will see radio logically whether it is going to be a CT scan of the brain or it should be chest, the lichens flatter very commonly you have seen in tuberculous of the brain. Autoimmune IRIS closely mimics the other I mean condition like (Refer Time: 06:24) syndrome more or less similar to that way off, but it is very rare.

What you need to know about irises is; it is not specific for any organism it is not specific to any specific location it is not specific to any ART. The mechanism is very simple and usually call it as the predetermined fury of the perturb immunity; the

immunity is already there this being restricted because of its inactivation once it is activated it starts throwing, it starts attacking the tissues and then that is how the inflammation is built up and that is how you get the syndrome.

Most important for us to know is once you diagnose IRIS the only objective sign of irises a reduction in viral load, other things are all subjective and can change. So, viral load in the program which has recently been introduced as a very important step which has been taken and we are thanks to that so that it is easy for us to diagnose IRIS and differentiate it from failure, does not require any specific treatment change all that it requires is anti-inflammatory drugs.

This is not unique to HIV alone; a patient on cardiac steroid therapy after that steroids are removed; a patient who is on a transplant or chemotherapy any immunosuppression can lead to what is called iris. Interestingly a patient was a virological failure started on second line drugs can even develop iris, this is what is important for you to know.

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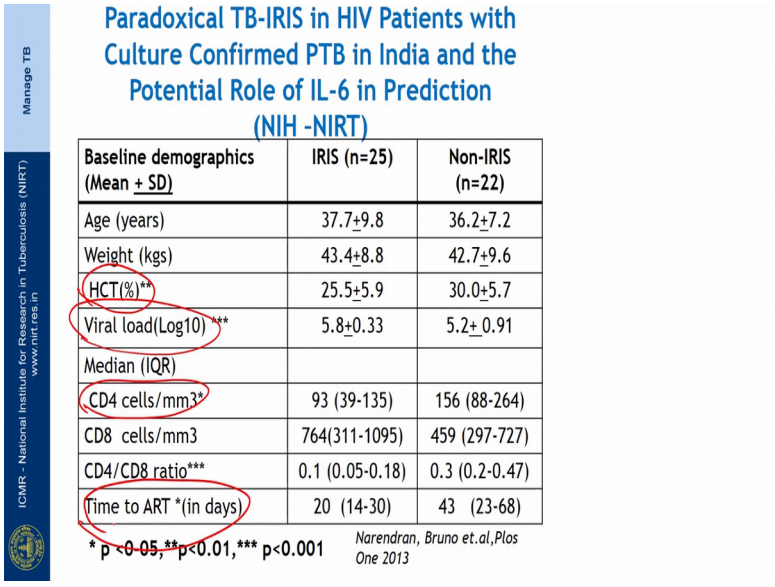

We had done a study with NIH in NIRT where we have found out clinical predictors of iris, what is the difference between patients or who are the patients were going to develop IRIS subsequently. We found that if the CD 4 is low or the viral load is high or

the hematocrit is very low these are the patients who are actually known prone for iris. These are not things which are modifiable, but what if what is modifiable is the time to ART.

I may be sounding paradoxical now because initially I told you that you start ART as early as possible, now I am telling you to delay ART; now which way should we go? The interesting aspect is that you start ART immediately. So, that the CD 4 does not drop down to the abyss as I told you earlier, but if in case the CD 4 is already drop down, if it is below 100 cells you need to council the patients regarding the benefits and risks of ART, you need to tell the patients to get hospitalised when they start ART.

But you cannot differ ART at because of the risk of IRIS as the benefits out either is, but whereas, a patient whose CD 4 is between 100 or more you can safely wait treat the specific continue the specific therapy like ATT, wait for the patient to stabilise before starting ART. This permissive delay has been very useful in preventing the unpleasant symptoms of IRIS so, that the patient can have a uneven full immune recovery.

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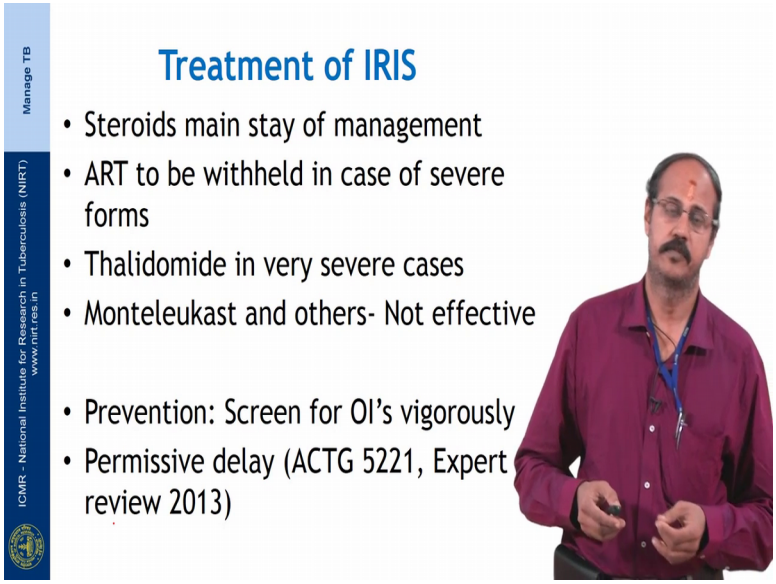

Looking at the treatment of IRIS steroids remain the main stay of management; interestingly the Indian population do not tolerate the 2 milligram of per kilogram

advocated in internationally, we have given 0.5 to 1 milligram of steroids and they have been useful in emulating the symptoms and signs of IRIS especially in non severe cases. In severe cases we may have to use parental steroids like hydrocortisone, methylprednisolone as well as decadron.

Thalidomide is used in severe cases except in women with of fertile age group and also in steroid dependent cases; please understand that if you start steroids at a very premature stage you can have recudo sense of symptoms or what we call it as an IRIS relapse. Many studies have shown that monteleukast is not effective in IRIS, maraviroc that cardiac trail very clearly stated that has no role in IRIS, so all these things are actually evolved.

How do you prevent one of the strategies of the program to start ART early in patient, once is diagnose HIV itself is a preventive measure because if you do not allow the CD 4 to go down you have the advantage that there is lesser toxicity and lesser IRIS. We have to screen for opportunistic infections vigorously because that is one way in which you can avoid this unpleasant uneventful and lead to uneventful recovery of immunity.

As I initially told you the permissive delay that is if the CD 4 is more than 100 you can wait up to the intensive phase of ATT, after the patient gets stabilise you can put the patients on ART and we parallely have the parallely accept the use of the ACTG 5221 trail and we have published that in expert review 2013.

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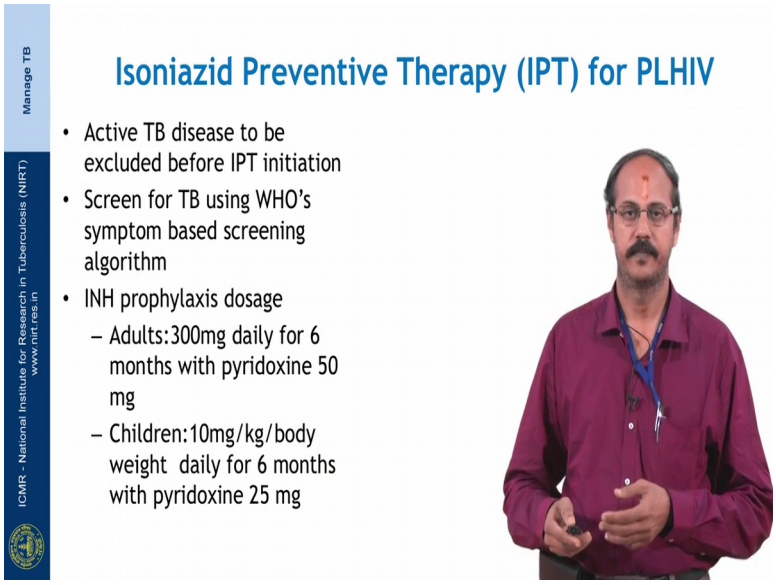

Coming to IPT, now IPT has the more of more awareness has been built on IPT both the temprano trail as well as the remember trail have shown that instead of empirical TB therapy, isoniazed preventive therapy has gone a long way in reducing TB breakdown. You have found in our trial in an ART the INH resistance because a patient breaks down to later day 2 TB is very very meagre; paralleling the findings other studies. The thing is the most important or oculus standard is to rule out active TB in a patient especially with advanced immunodeficiency, but this always as remind a grey area.

INH prophylaxis dosage what is the advocate is now 10 milligram per kg per body, pyridoxine is more importantly should be given, peripheral neuropathy in children is much more better tolerated than in adults, but you have to be very cautious while doing where giving it in children.

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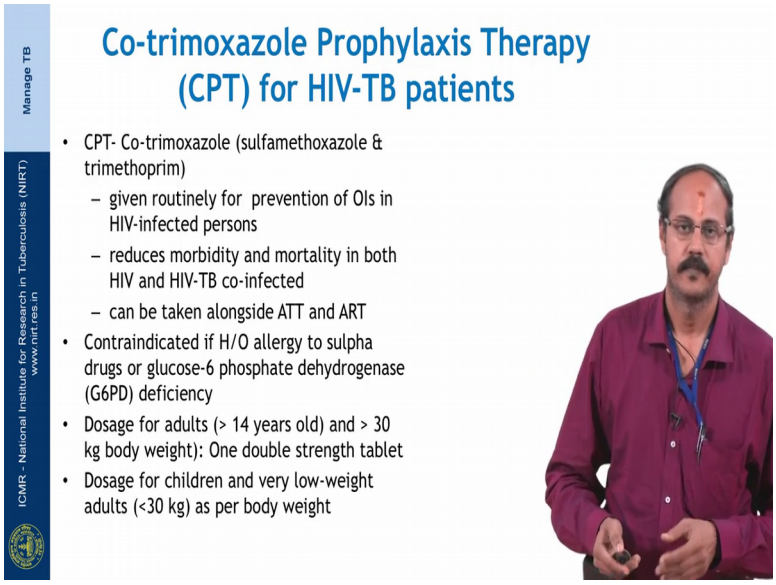

Co-trimoxazole prophylaxis is more important when the CD 4 is low. If the CD 4 has reason to a level and you repeat the CD 4 2 point 2 time points at least 3 months part and it is more than 500 cells you can you can always end the co-trimoxazole prophylaxis therapy. And this has been very helpful in reducing PCP, taxocara canis, cryptosporidium parvum as well as hemoplus influence. You have to remember that whenever a patient has allergy; the sulfanilide group has to be kept in mind, co-trimoxazole has been stop first, after that the nnrtas in that order.

Patients with G 6 PD deficiency also cannot have co-trimoxazole, when patients have zedovudine and co-trimoxazole together bone marrow suppression may be there and neutropenia may be there you have to be very careful about it. Jaundice patient you have to temporarily stop co-trimoxazole, apart from that usually it is well tolerated.

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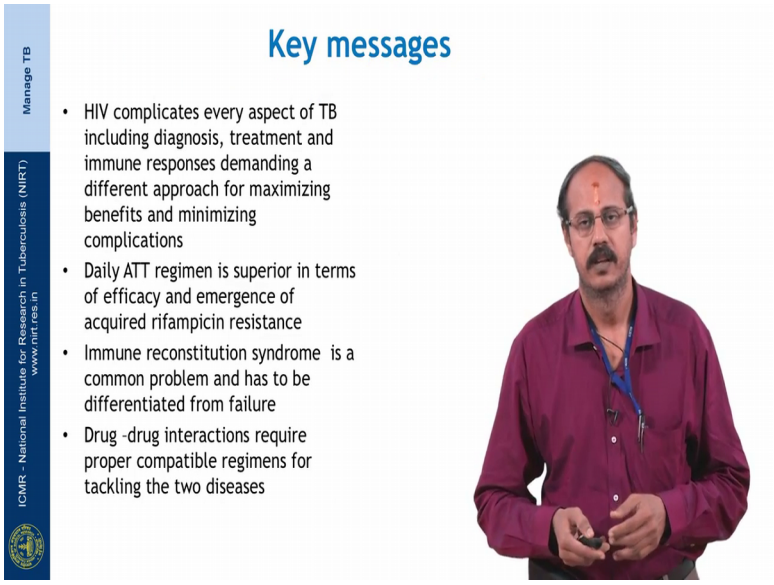

Just to summarise the findings you know that HIV complicates every aspect of TB, you need to have a different approach while you are trying to deal with these two conditions, they are perfect, complex. Daily regimen proves to be superior with respect to efficacy and more importantly it prevents emergence of drug resistance, especially if the intensive faces daily of course, a part daily regimen is not as good as a daily regimen which you have found out in a trail it is going to be published soon.

Immune reconstitution syndrome it is a very common problem you do not have to be jittery. You need to have know how differentiate it from failure, since now the program already has viral load and GeneXpert on its armamentarium. It is very easy for us to diagnose IRIS and differentiate it from failure; drug-drug interactions require proper dosing titration of doses so that we have much maximum efficacy out of them.

I thank you for the patience.

Thank you so much.