Original Research Article

MANAGEMENT OF TUBERCULOSIS - NTEP GUIDELINES

Tejinder Singh, Bankey Bihari, Sanjay Kumar Goyal, Sachin Kaushal, Sargam Bansal, Karuna, Pankaj kumar

Department of Medicine, Government Medical College, Patiala

Corresponding Author : Dr. Bankey Bihari
Junior Resident, Department of Medicine
Government Medical College, Patiala-147001, Punjab, India
Email: goyalbanki@gmail.com

Abstract

The year 2019 saw an estimate by WHO that 10 million fresh cases of TB emerged globally, with a staggering 97% of them emerging in low- & middle-income countries.[1] Among these cases, 57% were seen in men, 32% in women, and the remaining 11% in children. Shockingly, approximately 1.4 million fatalities were recorded due to TB that year, including around 0.21 million among individuals co-infected with HIV. In India, the burden of tuberculosis infection (TBI) is believed to be the highest globally, with an estimated range of 350-400 million individuals living with TBI. Of these numbers, roughly 2.6 million are reported as tuberculosis (TB) cases annually. TB ranks as the 13th leading cause of death on a global scale and continues to plague HIV-infected individuals. Management, diagnosis quality, and treatment services for tuberculosis under the program are provided free of charge nationwide with the vision of achieving a TB-free India by 2025. The typical drug regimen for Tuberculosis includes an intensive two-month phase followed by a four-month continuation phase. However, the duration of treatment may vary based on severity/organ involvement, necessitating tailored regimens in certain cases such as those involving pregnant women or issues with liver or kidney function as per NTEP guidelines.

INTRODUCTION

Coming from the Mycobacteriaceae family and Actinomycetes order, Mycobacteria has eight distinct groups within the Mycobacterium tuberculosis complex. Of these groups, Mycobacterium tuberculosis is highlighted as the primary agent causing human disease among pathogenic bacteria within this complex. Typically affecting the lungs but potentially spreading to other organs in up to one-third of cases.

PRESUMPTIVE TB CASE:

An individual exhibiting signs like cough lasting over two weeks, prolonged fever, significant weight loss, blood-stained sputum coughed up from the lungs (hemoptysis), night sweats, or any anomalies detected in chest X-rays might be considered a presumptive TB case.

TUBERCULOSIS INFECTION (TBI):

Individuals who show persistent immune responses towards M. tuberculosis antigens without any clear evidence of active TB disease are considered to have TBI or latent TB [LTBI]. Tests like TST and IGRA help assess LTBI.[8]

TUBERCULOSIS (TB) DISEASE:

This condition manifests itself when someone infected with M. tuberculosis showing symptoms or signs suggestive of TB disease.

MULTI DRUG RESISTANT –TB:

MDR-TB arises from strains resistant at least to Isoniazid and Rifampicin – anti-TB drugs with potential resistance to other first-line anti-TB medications too.[2]

WHO's Recently Published Definitions include:

Pre-XDR-TB: MDR/RR-TB Mycobacterium tuberculosis strains additionally resistant to any fluoroquinolones.[2]

XDR-TB: This refers to MDR/RR-TB strains showing additional resistance to any fluoroquinolone along with at least one more Group A drug including levofloxacin/moxifloxacin coupled with bedaquiline & linezolid.[2]

RESISTANCE	TO
H MONO DRUG RESISTANTANCE	ISONIAZID ONLY (M/C)
MDR TB	Atleast resistant ISONIAZID + RIFAMPICIN
RIFAMPICIN RESISTANT TB	RIFAMPICIN ONLY
PRE- XDR TB	MDR+ ANY FLOROQUINOLONE
XDR TB	MDR+ ANY FLOROQUINOLONE + ANY GROUP A DRUGS

CURED:

A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment and followed the national treatment policy has been deemed Cured if they show evidence of bacteriological response and no signs of treatment failure.[3]

LOST TO FOLLOW UP:

A patient who failed to commence treatment or had their treatment discontinued for a consecutive month or more is classified as Lost to follow-up.

TREATMENT FAILED:

For a patient whose treatment regimen was altered permanently or needed to be stopped due to inefficacy, it is considered Treatment failed.

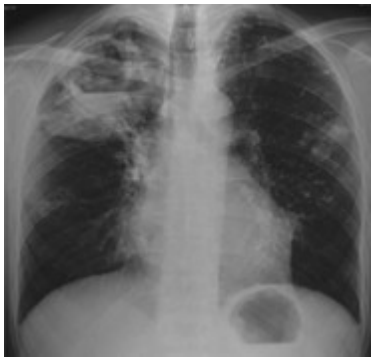
TREATMENT COMPLETED:

One who complies with the national policy's prescribed treatment and does not fit the criteria for cure or treatment failure is labeled Treatment completed.

SPREAD:

The most contagious form of tuberculosis involves cavitary pulmonary disease or, less commonly, laryngeal TB, wherein sputum may contain as many as 105–107 AFB/mL Bacilli - this can persist for years before reactivating, typically resulting in secondary (or postprimary) TB. This form is more infectious than primary disease due to the frequent presence of cavities. Approximately 10% of infected individuals are projected to develop active TB during their lifetime, with half within the first 18 months following infection - especially enhanced among immunocompromised individuals and those with HIV. In many cases, lesions from TB naturally heal and become evident only through small calcified nodules. Pleural reactions involving subpleural focuses are common - also known as the Ghon complex when associated with lymphadenopathy. Pleural effusion is prevalent in up to two-thirds of cases, often stemming from bacilli entering the pleural space from neighboring subpleural areas. In severe instances, primary sites may necrose centrally, leading to cavitation – termed as progressive primary TB.

POSTPRIMARY (ADULT-TYPE) DISEASE - also known as reactivation or secondary TB - predominantly affects apical and posterior segments of upper lobes due to higher oxygen tension in these regions compared to lower zones.



In about 90% of cases, cough develops eventually, possibly starting off as nonproductive and confined to mornings before progressing to purulent sputum production - at times including blood streaks. Hemoptysis arises in 20-30% cases, occasionally culminating in massive bleeding from vessel erosion within cavity walls (Rasmussen's aneurysm) or due to aspergilloma formation within cavities.

Patients may experience pleuritic chest pain in instances of subpleural parenchymal lesions or pleural involvement. Extensive disease could lead to dyspnea, while acute respiratory distress syndrome (ARDS) may occur rarely.

MANAGEMENT OF PULMONARY TB[6]

Type	Treatment Regimen in IP	Treatment Regimen in CP
Previously treated and New cases (H and R Sensitive)	2HRZE	4HRE

Diagnostic Modalities:

1. Chest X-ray: Not very specific, can see cavities.
2. Sputum for AFB: Take 5ml of sputum, test within 24 hrs. Two samples taken: a spot sample and a morning sample. If any one sample is positive, sputum is taken as positive. NAAT is more sensitive than sptum for AFB.

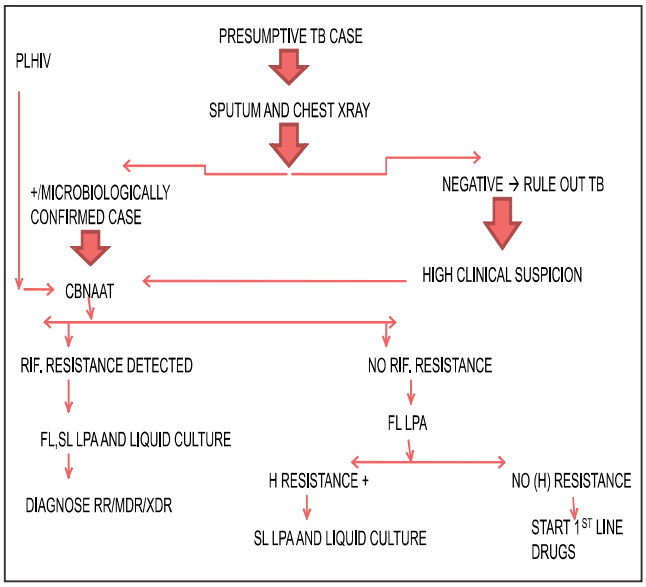
3. CBNAAT: Test results in 2 hrs, provides Rifampicin sensitivity status. Highly sensitive and specific as it shows much less false negative results even in paucibacillary cases.

EXTRAPULMONARY SAMPLES	CBNAAT SENSITIVITY
CSF	71%
LYMPH NODES	82%
PLEURAL FLUID	50%
PERITONEAL FLUID	59%

4. TruNAAT: Local device, cheaper (used for TB diagnosis in India). It also tells about the Rifampicin sensitivity. Trunaat result also takes 2 hours, 1 hour for MTB detection and 1 hour for R sensitivity if MTB detected.
5. LPA: Results in 3 days.
6. Culture:

* Liquid culture (LC): Gold standard, results in 2-4 weeks
* (LJ media) Solid culture: Results in 6-9 weeks.

Algorithm for management of Presumptive TB case[5]:



WEIGHT BANDS OF FDC IN ADULTS:

WEIGHT (KGS)	NO. OF FDC TABLETS (HRZE) - 75/150/400/275MG
25-34	2
35-49	3
50-64	4
65-75	5
>75	6

DRUG DOSAGE OF FIRST LINE ATT IN ADULTS:

DRUGS	ADULT DOSAGE
ISONIAZID	5 mg/kg daily
RIFAMPICIN	10 mg/kg daily
PYRAZINAMIDE	25 mg/kg daily
ETHAMBUTOL	15 mg/kg daily
STREPTOMYCIN	15mg/kg daily

REGIMEN FOR TREATMENT OF DRUG SENSITIVE AND DRUG RESISTANT TB:[8]

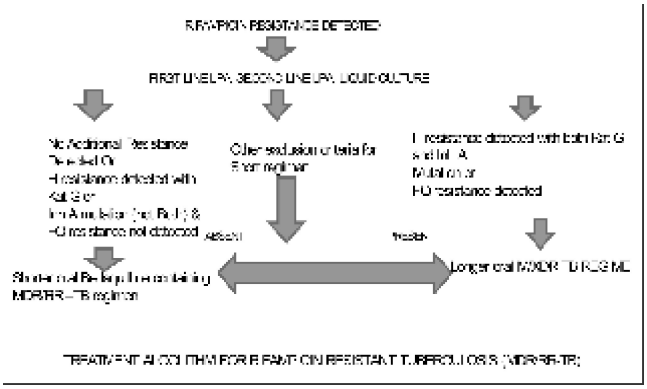
Management of TB:		
Regimen class	*Intensive phase*	*Continuation phase*
	DSTB(Drug sensitive TB)	
DSTB	HRZE(2 months) Isoniazid (H) Rifampicin(R) Ethambutol(E) Pyrazinzmide(Z)	HRE (4 months)
	DRTB(Drug resistant TB)	
H mono/poly DR-TB	ZERO(6 months) [o-levoflox]	
Shorter MDR/RR-TB	CHOBZEE(4-6 months) Clofazimine High dose Isoniazid Levofloxacin(o) Bedaquiline Pyrazinamide Ethambutol Ethionamide	COZE(5 months) Clofazimine Levofloxacin Pyrazinamide Ethambutol

Longer MDR	C2 L2 B(18-20 months) (oral regimen) Levofloxacin Linezolid Bedaquiline Cycloserine Clofazimine

In Longer MDR regime, Linezolid to be reduced to 300 mg after 6-8 months of treatment. Give Bedaquiline for 6 months and in exceptional cases can be given for more than 6 months

1st line drugs	Activity	CSF Penetration
Pyrazinamide	Cidal	95-100%
Isoniazid	Cidal	90-95%
Ethambutol	Static	10-50%
Streptomycin	Cidal	10-20%
Rifampicin	Cidal	5-25%

2nd line drugs	Activity	CSF Penetration
Linezolid	Cidal	80-100%
Ethionamide	Cidal	80-95%
Moxifloxacin	Cidal	70-80%
Levofloxacin	Cidal	60-80%
Cycloserine	Static	40-70%
Amikacin	Cidal	10-25%
Kanamycin	Cidal	0-43%



Dosage for shorter oral bedaquilline containing MDR/ RR-TB regimen for adults

SN	Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
1	High dose H (H*)	300 mg	600 mg	900 mg	900 mg
2	Ethambutol(E)	400 mg	800 mg	1200 mg	1600 mg
3	Pyrazinamide(Z)	750 mg	1250 mg	1750 mg	2000 mg
4	Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg
5	Bedaquiline (Bdq)	Week 0–2: Bdq 400 mg daily			
		Week 3–24: Bdq 200 mg 3 times per week			

SN	Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
6	Clofazimine (Cfz)	50 mg	100 mg	100 mg	200 mg
7	Ethionamide (Eto)*	375 mg	500 mg	750 mg	1000 mg
8	Pyridoxine (Pdx)	50 mg	100 mg	100 mg	100 mg

*Drugs can be given in divided doses in a day in the event of intolerance

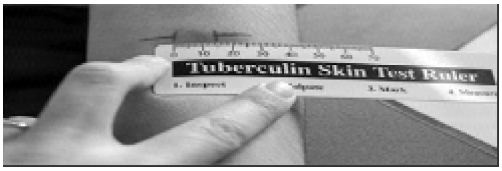
TREATMENT DURATION OF MEDICAL THERAPY IN EXTRAPULMONARY TUBERCULOSIS:

Site of Disease	Initial Regimen (IIP + CP)	Duration
Ocular TB	(2)HRZE + (4-7)HRE	6-9 Months
CNS TB	(2)HRZ+E/S + (10)HRE	6-12 Months
Tuberculous Otitis Media	(2)HRZE + (7)HRE	9 Months
Ear, Nose and Throat TB (Others)	(2)HRZE + (4-7)HRE	6-9 Months
Lymph node TB	(2)HRZE + (4-7)HRE	6-9 Months
Pleural TB	(2)HRZE + (4)HRE	6 Months
Pericardial TB	(2)HRZE + (4)HRE	6 Months
*Hepatobiliary TB	(2)HRZE+(4-7)HRE	6-9 Months
Intestinal TB	(2)HRZE + (4)HRE	6 Months
Urinary TB	(2)HRZE + (4)HRE	6 Months
Genital TB (Male or Female)	(2)HRZE + (4)HRE	6 Months
Spinal TB	(2)HRZE + (10-16)HRE	12-18 Months
Bone and Joint TB (others)	(2)HRZE + (10)HRE	12 Months
Cutaneous TB	(2)HRZE + (4)HRE	6 Months

H – Isoniazid, R – Rifampicin, Z – Pyrazinamide, E – Ethambutol, S – Streptomycin, Amikacin
*Treatment may be modified according to stage of Liver Disease. Refer below

TUBERCULIN SENSTIVITY TEST :

During the diagnosis of TB in children, the Tuberculin skin test serves as a helpful tool. Remember to use the standard product PPD RT23 with tween 80 and not exceed two tuberculin units for an accurate reaction to M.tb.



Indication of 10mm or more after 48-72 hours post-tuberculin indicates TB infection.

SKELETAL TB:

* Bone and joint disease pathogenesis involves reactivation from hematogenous foci or spreading from nearby paravertebral lymph nodes.
* Weight-bearing joints are commonly affected with spinal TB (Pott's disease).[3]
* In children, upper thoracic spine is a common site, while adults typically show lower thoracic and upper lumbar vertebrae involvement.

Drug therapy according to INDEX-TB guideline for drug-susceptible spinal TB comprises:

2HRZE + 10 HRE

Duration: 12 months extensible based on individual cases

Spinal surgery indications include:

1. Neurological deficit:

* Neural complications worsening during non-operative treatment
* Sudden onset paraplegia
* Severe neurological deficits like flaccid paraplegia, complete sensory/motor loss, bowel/bladder incontinence, painful paraplegia in elderly

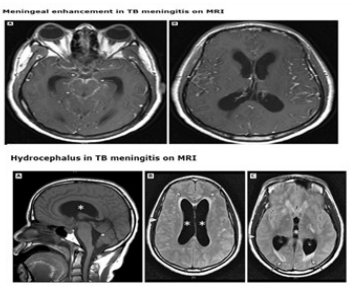
2. Absence of neurological deficit:

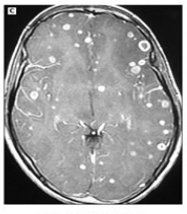
Uncertain diagnosis requiring open biopsy, mechanical spine instability

TUBERCULOUS MENINGITIS AND TUBERCULOMA :

About 5% of extrapulmonary cases involve the Central Nervous System. Tuberculous meningitis occurs if there is spread from pulmonary TB or rupture of subependymal tubercle .[4]Common symptoms include severe headache, confusion, lethargy, altered sensorium, neck rigidity. CSF analysis shows high leukocyte count (up to 1000/μL), elevated protein content (1–8 g/L)or 100-800 mg/dl, low glucose.

Immediate treatment initiation upon positive Xpert MTB; negative result does not rule out TB diagnosis and warrants further evaluation.

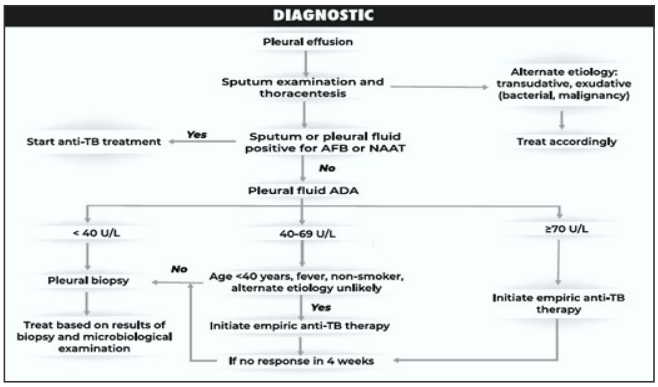




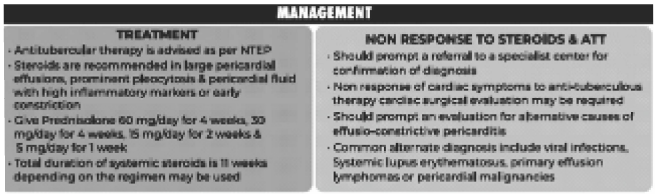
TUBERCULOMA

During the intensive phase of treatment of TBM , patients receive RHZE or RHZS for two months. In the continuation phase, they take RHE for a minimum of seven months or RHZ at least ten months. If a patient vision is problematic or cannot be evaluated, streptomycin should be used instead of ethambutol in the intensive phase. Close monitoring every month for the initial three months is crucial, with possible increases in frequency afterward until treatment completion. Intravenous Dexamethasone is administered at 0.4 mg/kg/24hrs in 3–4 split doses. Following this, patients are discharged on oral steroids with gradually decreasing doses over a total period of 8-12 weeks, with a minimum of 4 weeks of treatment.

PLEURAL EFFUSION:

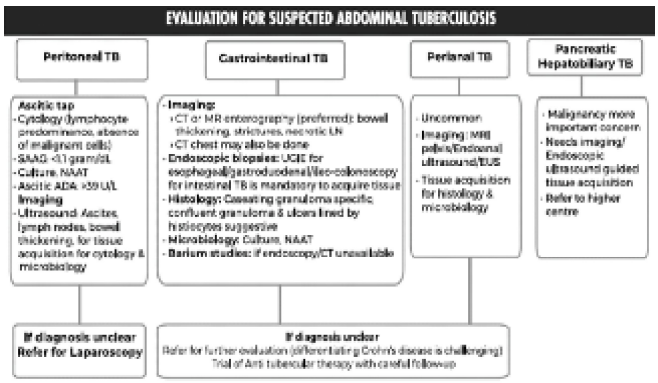


MANAGEMENT OF PERICARDIAL TB:



ABDOMINAL TB

Extrapulmonary TB =15–20% TB cases
Abdominal TB =3% Extrapulmonary TB
Tuberculosis can involve any part of GIT



PARADOXICAL REACTION:

Paradoxical reaction, refers to a worsening of existing tuberculous lesions or the appearance of new lesions in patients on anti-tubercular medication who initially showed improvement.

The deterioration within the first 3 weeks to 4 months may be attributed to a paradoxical reaction. This phenomenon has been noted in both HIV-positive and negative TB patients over the years.

It is crucial rule out other reasons for clinical decline. PR is more prevalent among HIV-infected individuals, especially within 2 months of starting combination antiretroviral therapy.

Management involves continuing the anti-tubercular treatment, providing symptomatic relief, using NSAIDs for pain, and considering USG-guided aspiration in case of fluctuance.

IRIS

Moving on to IRIS, immune reconstitution inflammatory syndrome occurs in HIV-positive individuals after starting antiretroviral therapy. It is triggered due to immune response reconstitution by an inflammatory response to an antigen .Patients with HIV and TB face a high risk of developing IRIS, which can sometimes be life-threatening. To minimize this risk, it is recommended to begin Anti-Tubercular Therapy before initiating Antiretroviral Treatment:

IRIS can manifest in two main ways: paradoxical TB-IRIS and unmasking TB-IRIS. Treatment typically involves starting ART after 3 weeks of beginning ATT and administering steroids if necessary.

BPAL REGIMEN:

Under operational research conditions, MDR-TB patients with TB resistant to fluoroquinolones who have either not previously been exposed to bedaquiline and linezolid or have only been exposed for a maximum of two weeks may benefit from a treatment regimen consisting of BEDAQUILINE, PRETOMANID, AND LINEZOLID (BPAL) that lasts six to nine months [7].

SPECIAL SITUATIONS:

PREGNANCY:

Before beginning tuberculosis treatment, it is crucial to inquire about pregnancy plans or current

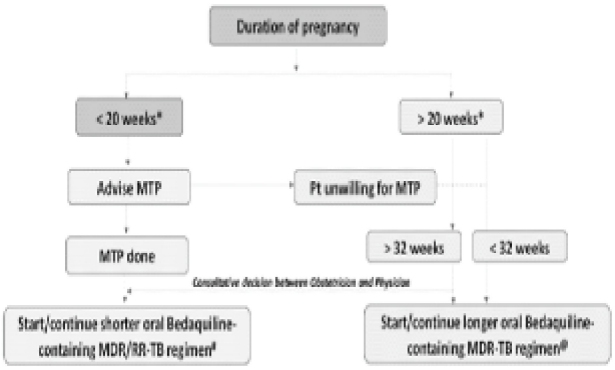
pregnancy from women of childbearing age and offer appropriate counseling. The successful treatment of TB significantly impacts the outcome of pregnancy. With the exception of streptomycin, the primary anti-TB medications are safe to use during pregnancy . Aminoglycosides should be avoided due to their teratogenicity during pregnancy.

Certain drugs like streptomycin, prothionamide, ethionamide, and quinolones are contraindicated in pregnancy.[10]

While Pyrazinamide usage is limited in the US due to safety concerns, WHO recommends its use as part of standard TB treatment for pregnant patients.

Although some drugs may pass into breast milk, breastfeeding can usually continue as these drugs rarely reach toxic levels. It's generally safe for mothers on medication to breastfeed their infants.

DR-TB IN PREGNANCY:



There is a significant risk to both mother and fetus upon treatment of DR resistant TB. However, it is important to note that, pregnancy itself is not a reason to avoid treatment. During pregnancy, second-line injectables should be avoided since they can affect the 8th cranial nerve of the fetus. Ethionamide should also be avoided in the first 32 weeks of pregnancy due to its potential harmful effects on the developing baby.

For pregnant women with drug-resistant TB, the shorter oral bedaquiline-containing regimen cannot be used. Instead, WHO recommends tailoring a longer oral M/XDR-TB regimen based on individual needs and safety considerations.

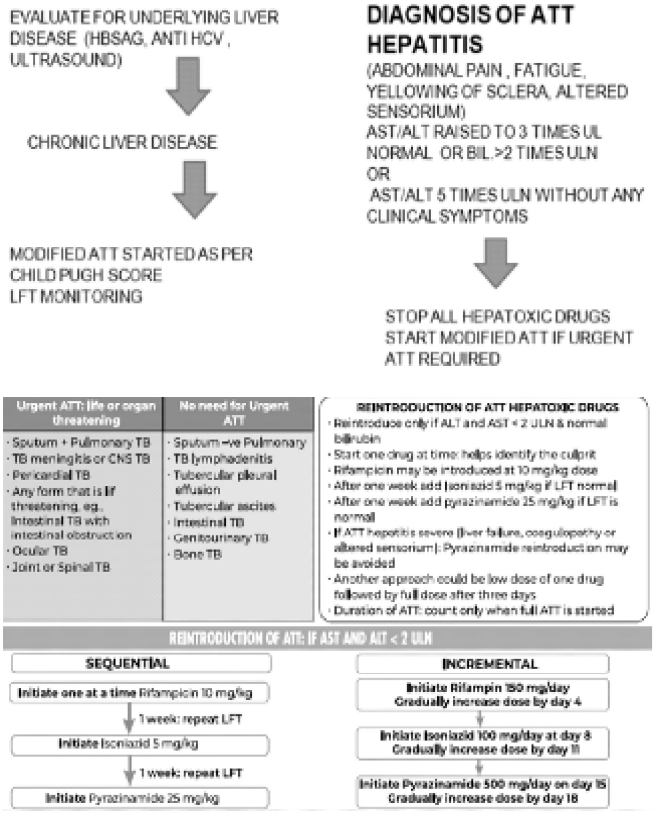
CONTRACEPTION:

When it comes to contraception, rifampicin and rifapentine can impact the effectiveness of oral or hormonal contraceptives. Women on these medications should consider alternative contraception methods like depot medroxyprogesterone acetate every eighth week or higher dose estrogen in consultation with a healthcare provider. For those with hormonal contraceptive implants, the timing for replacement may need adjustment from 12 weeks to eight weeks.

CHRONIC LIVER DISEASE :

In patients with chronic liver disease:

* When with acute hepatitis alongside a non-life-threatening EPTB, it's okay to wait on starting treatment until liver tests come back normal. If EPTB is serious, like CNS-TB, go for a modified ATT.
* The number of drugs that might harm the liver in this situation depends on how the liver disease is. The main drugs in the first line of treatment are Pyrazinamide (Z), Isoniazid (H), and Rifampicin (R). Sometimes, fluoroquinolones can also lead to hepatitis.[11]
* Patients who have had acute hepatitis or jaundice in the past don't need any changes to their standard first-line treatment.



CHILD PUGH (CTP) SCORE			
	Score 1	Score 2	Score 3
Bilirubin	<2 mg/dl	2-3 mg/dl	>3 mg/dl
Albumin	>3.5 gm/dl	2.8-3.5 gm/dl	<2.8 gm/dl
INR	<1.7	1.7-2.2	>2.2
Ascites	Absent	Slight	Moderate
Encephalopathy	Absent	Grade 1-2	Grade 3-4

HEPATIC ENCEPHALOPATHY GRADE
- Grade 0: normal consciousness, personality & neurological examination
- Grade 1: restless, disturbances in sleep, irritability or agitated, tremors, handwriting affected
- Grade 2: lethargy, disorientation to time, asterixis, ataxia
- Grade 3: somnolent & stuporous, disoriented to place, hyperactive reflexes, rigidity
- Grade 4: unrousable coma, decerebrate

ATT SELECTION FOR UNDERLYING LIVER DISEASE	
Child Status	Suggested ATT
Child A Cirrhosis (Score 1-6) Stable Liver disease	9 months of therapy with HRE OR 2 months of therapy with HRE followed by 7 months of HR
Child B Cirrhosis (Score 7-10) Advanced Liver Disease	One hepatotoxic drug regimen can be used: Two months of therapy with INH (or) RIF with ETH & aminoglycoside, followed by 10 months of therapy with INH/RIF & ETH
Child C Cirrhosis (Score 11-15) Very advanced liver disease	No hepatotoxic drug 18 to 24 months treatment using a combination of ETH, FQL, cycloserine & aminoglycoside/ capreomycin
In Acute hepatitis	Avoid hepatotoxic drugs ATT with non-hepatotoxic drugs if urgent ATT required Wait till improvement in liver function if no urgent need of ATT

CHRONIC RENAL DISEASE:

Patients who have Chronic Kidney Disease (CKD) may starting anti-tubercular therapy (ATT). It is essential to be cautious when administering aminoglycoside drugs in these situations. Reduced creatinine clearance can result in the buildup of certain medications, leading to toxicity. Some drugs might be removed during hemodialysis, causing reduced serum levels and potential under-dosing.

Isoniazid and rifampicin are excreted through bile, so no alterations in dosages are needed. Ethambutol and pyrazinamide metabolites are significantly excreted through the kidneys, necessitating dosage adjustments.[9]

Recommended dosage of ATT drugs in ckd:

Drug*	Recommended dose in patients with creatinine clearance <30ml/min
Rifampicin	No adjustment in dose required
Isoniazid	No adjustment in dose required
Pyrazinamide	Recommended dose given three times per week (NOT DAILY)
Ethambutol	Recommended dose given three times per week (NOT DAILY)
Streptomycin	12-15 mg/kg per dose two or three times per week (NOT DAILY)

* Administer the drugs after the dialysis session on the day of haemodialysis.

Adjustment of anti-TB drugs in renal insufficiency	
Drug	Recommended dose and frequency for patients with creatinine clearance < 30 ml/min or for patients receiving hemodialysis (unless otherwise indicated dose after dialysis)
Pyrazinamide	25-35 mg/kg per dose three times per week (not daily)
Ethambutol	15-25 mg/kg per dose three times per week (not daily)
Rifabutin	Normal dose can be used, if possible monitor drug concentrations to avoid toxicity.
Streptomycin	12-15 mg/kg per dose two or three times per week (not daily)*
Capreomycin	12-15 mg/kg per dose two or three times per week (not daily)*
Kanamycin	12-15 mg/kg per dose two or three times per week (not daily)*
Amikacin	12-15 mg/kg per dose two or three times per week (not daily)*
Ofloxacin	600-800 mg per dose three times per week (not daily)
Levofloxacin	750-1000 mg per dose three times per week (not daily)
Cycloserine	250 mg once daily, or 500 mg / dose three times per week*
Para-aminosalicylic acid*	4 g/dose, twice daily maximum dose*
Moxifloxacin	No dose adjustment is necessary

Drug	Recommended dose and frequency for patients with creatinine clearance < 30 ml/min or for patients receiving hemodialysis (unless otherwise indicated dose after dialysis)
Imipenem / cilastin	For creatinine clearance 20-40 ml/min dose 500 mg every 8 hours; For creatinine clearance <20 ml/min dose 500 mg every 12 hours
Meropenem	For creatinine clearance 20-40 ml/min dose 750 mg every 12 hours; For creatinine clearance <20 ml/min dose 500 mg every 12 hours
Amoxicillin/clavulanate	For creatinine clearance 10-30 ml/min dose 1000 mg as amoxicillin component twice daily; For creatinine clearance <10 ml/min dose 1000 mg as amoxicillin component once daily

PEOPLE LIVING WITH HIV:

Patients diagnosed with HIV should prioritize beginning TB treatment following the NTEP guidelines. Antiretroviral therapy (ART) needs to commence 2 weeks after starting anti-TB treatment (ATT) and within 8 weeks at the latest. ART and ATT should be started together , if CD4 count are below 50 cells/mm3,. All newly diagnosed co-infected patients must receive a fixed-dose combination of TLE single pill based regimen, regardless of their hemoglobin levels or CD4 count.

Condition	Alternate First-line Regimen
PLHIV with body weight <30 kg	ABC 600 mg + Lamivudine 300mg, one tablet + DTG (50 mg) once daily in the morning or any fixed time every day as per patient's convenience
All patients with high (above ULN for laboratory) serum creatinine values (Calculate Creatinine clearance)	ABC 600 mg OD. Lamivudine (as per creatinine clearance**) and DTG 50 mg once daily in the morning or any fixed time every day as per patient's convenience
PLHIV on Rifampicin-containing ATT regimen	Tenofovir (300 mg) + Lamivudine (300 mg) + Dolutegravir (50 mg) – FDC one tablet once daily (in the morning or any fixed time every day as per patient's convenience) + Additional dose of DTG 50 mg to be provided (12 hours after taking their regular dose) until 2 weeks after completion of ATT
Women of childbearing potential who do not wish to take DTG-based ART after adequate and optimal counselling***	Tenofovir (300 mg) + Lamivudine (300 mg) + Efavirenz (600mg) If Efavirenz is contraindicated (HIV-2/HIV-1&2/prior NNRTI exposure) then Tenofovir (300 mg) + Lamivudine (300 mg) + [Lopinavir (200 mg) + ritonavir (50 mg) twice daily]

*For all patients with high serum creatinine values (above ULN for laboratory), calculate creatinine clearance.

**Lamivudine, along with Abacavir, may be used in full dose if creatinine clearance is more than 30 ml per minute, with patient being closely monitored.

***Women of childbearing potential receive full information and medical guidance that is appropriate to their situation and are supported in making an informed decision.

While efavirenz can be combined with rifampicin or rifapentine without adjusting the dosage, PLHIV on raltegravir and rifampicin should take a higher dose of raltegravir (800 mg twice daily). It's important not to mix rifampicin or rifapentine TPT regimens with protease inhibitors (atazanavir/ritonavir, lopinavir/ritonavir) or nevirapine for individuals living with HIV.

REFERENCES:

1. Chakaya J, et al. Global Tuberculosis Report 2020–Reflections on the Global TB burden, treatment and prevention efforts. International journal of infectious diseases. 2021 Dec 1;113:S7-12. Deelder W, et al. A modified decision tree approach to improve the prediction and mutation discovery for drug resistance in Mycobacterium tuberculosis. BMC genomics. 2022 Jan 11;23(1):46.
2. Diriba G, Alemu A, Yenew B, Tola HH, Gamtesa DF, Mollalign H, Eshetu K, Moga S, Abdella S, Tollera G, Kebede A, Dangisso MH. Epidemiology of

extensively drug-resistant tuberculosis among patients with multidrug-resistant tuberculosis: A systematic review and meta-analysis. Int J Infect Dis. 2023 Jul;132:50-63. doi: 10.1016/j.ijid.2023.04.392. Epub 2023 Apr 16. PMID: 37072053; PMCID: PMC10302157.

3. Pande A. Pulmonary tuberculosis presenting acutely as paraplegia: An unusual presentation. Journal of Family Medicine and Primary Care. 2013 Jul 1;2(3):294-5.
4. Nikita Suryakant Vasava, et al. A rare case of generalized tuberculosis in 29yr old female including multiple tuberculoma with tuberculous arteritis with tubercular meningitis associated with acute cerebellar infarction and hypersensitivity reaction to the first line anti tubercular treatment in post partum period .2024
5. Suárez I, Fünger SM, Kröger S, Rademacher J, Fätkenheuer G, Rybniker J. The diagnosis and treatment of tuberculosis. Deutsches Aerzteblatt International. 2019 Oct 25;116(43).
6. Borah P, Deb PK, Venugopala KN, Al-Shar'i NA, Singh V, Deka S, Srivastava A, Tiwari V, Mailavaram RP. Tuberculosis: an update on pathophysiology, molecular mechanisms of drug resistance, newer anti-TB drugs, treatment regimens and host-directed therapies. Current Topics in Medicinal Chemistry. 2021 Feb 1;21(6):547-70.
7. Günther G, Ruswa N, Keller PM. Drug-resistant tuberculosis: advances in diagnosis and management. Current opinion in pulmonary medicine. 2022 May 1;28(3):211-7.
8. Kiazyk S, Ball TB. Latent tuberculosis infection.
9. Alemu A, Bitew ZW, Diriba G, Seid G, Eshetu K, Chekol MT, Berhe N, Gumi B. Tuberculosis incidence in patients with chronic kidney disease: a systematic review and meta-analysis. International Journal of Infectious Diseases. 2022 Sep 1;122:188-201.
10. Miele K, Morris SB, Tepper NK. Tuberculosis in pregnancy. Obstetrics & Gynecology. 2020 Jun 1;135(6):1444-53.
11. Soedarsono S, Riadi AR. Tuberculosis drug-induced liver injury. Jurnal Respirasi. 2020 May 30;6(2):49-54.