NATIONAL ANTIBIOTIC GUIDELINES 2016

Department of Health

NATIONAL ANTIBIOTIC GUIDELINES

PUBLIC HEALTH PROGRAM

(Tuberculosis)

TUBERCULOSIS (TB)

The available anti-TB drugs are:

- First Line anti-TB drugs: Rifampicin (R), Isoniazid (H), Ethambutol (E), Pyrazinamide (Z), and Streptomycin (S)
- Second line anti-TB drugs: Levofloxacin (Lfx), Moxifloxacin (Mfx), Kanamycin (Km), Capreomycin (Cm), Prothionamide (Pto), Cycloserine (Cs), Linezolid (Lzd), Clofazimine (Cfz), Bedaquiline (Bdq), Para-aminosalicylic Acid (PAS) and Imipenem (Imp). These drugs will only be used in certified PMDT centers.

Anti-TB drugs in fixed-dose combination (FDC) preparation.

- Adult FDC tablet: Contains isoniazid 75 mg and rifampicin 150mg, +/- pyrazinamide 400 mg, +/-ethambutol 275 mg per tablet.
- Pediatric FDC dispersible tablet: Contains isoniazid 50 mg and rifampicin 75 mg, +/- pyrazinamide 150 mg per tablet. Give the entire daily dose once a day.

Single-drug formulations (SDF) are still recommended for the following situations: adverse reactions or at risk for adverse reactions; co-morbid conditions requiring dose adjustments (especially liver, kidney diseases); or expected to have significant drug interactions. However, local availability of SDFs is poor.

	PREFERRED REGIMENS	COMMENTS
Category I Pulmonary TB, New (no treatment or had undergone previous treatment for less than a month; whether bacteriologically confirmed or clinically diagnosed) Miliary TB without dissemination or with dissemination not involving meningitis, bones, joints Extrapulmonary TB (EPTB), New (whether bacteriologically confirmed or clinically diagnosed) EXCEPT CNS, bones, joints	**P (<15y):**	ALL children being treated for TB should be weighed at least once every month to allow for adjustment of dosage(s). All patients should be weighed monthly for possible dose adjustments. Anti-TB treatment shall be done through a patient-centered, Directly-Observed Treatment (DOT) to foster adherence. Anti-TB treatment regimen shall be based on anatomical site and bacteriologic status including drug resistance and history of prior treatment, as well as the presence of co-morbid conditions. A patient's anti-TB regimen shall be comprised of at least four (4) first-line drugs. Fixed dose combination (FDC) should be used even for children. Single drug formulation should be used for specific subsets of patients such as those with hypersensitivity reactions to rifampicin and other anti-TB drugs: drug reactions; hepatic or renal impairment.

Body weight	Intensive phase (2 mos. HRZE) (No. of tablets)		Continuation phase (4 mos. HR)
	HRZ	E (100 mg)	HR
4-7 kg	1	1	1
8-11 kg	2	2	2
12-15 kg	3	3	3
16-24 kg	4	4	4
25+ kg	Adult dose and preparations		

A:

Body weight	Intensive phase (2 mos. HRZE) (No. of tablets)	Continuation phase (4 mos. HR)
	HRZE	HR
30-37 kg	2	2
38-54 kg	3	3
55-70 kg	4	4
>70 kg	5	5

Drug Dosage per kg body weight (if using single-drug formulations)

Anti-TB drug	Pediatric		Adult	
	Dose (mg/kg BW)	Max dose/d (mg)	Dose (mg/kg BW)	Max dose (mg/d)
Isoniazid	10 (10-15)	300	5 (4-6)	400
Rifampicin	15 (10-20)	600	10 (8-12)	600
Pyrazinamide	30 (20-40)	2,000	25 (20-30)	2,000
Ethambutol	20 (15-25)	1,200	15 (15-20)	1,200

Refer to Table below on Summary of treatment regimens for EPTB.

Category Ia
2HRZE/10HR

Extra-pulmonary TB (EPTB), New: CNS, bones or joints

P (<15y):

Body weight	Intensive phase (2 mos. HRZE) (No. of tablets)		Continuation phase (10 mos. HR)
	HRZ	E (100 mg)	HR
4-7 kg	1	1	1
8-11 kg	2	2	2
12-15 kg	3	3	3
16-24 kg	4	4	4
25+ kg	Adult dose and preparations		

Referral to relevant specialties is recommended for EPTB.

Use of corticosteroids as adjunctive therapy is recommended ONLY for patients with TB meningitis and/or TB pericarditis.

- TB meningitis: Dexamethasone 0.4mg/kg/24h with a reducing course over 6-8 weeks
- TB pericarditis: Prednisolone 60 mg for the first 4 weeks, 30 mg for weeks 5-8, 15 mg for weeks 9-10 and 5 mg for week 11.

A:

Body weight	Intensive phase (2 mos. HRZE) (No. of tablets)	Continuation phase (10 mos. HR)
	HRZE	HR
30-37 kg	2	2
38-54 kg	3	3
55-70 kg	4	4
>70 kg	5	5

Refer to Table below on Summary of treatment regimens for EPTB.

Category II
2HRZES/ 1HRZE/5HRE

PTB or EPTB, previously treated drug-susceptible TB (whether bacteriologically-confirmed or clinically-diagnosed)

- Relapse
- Treatment After Failure
- Treatment After Lost to Follow-up (TALF)
- Previous Treatment Outcome Unknown
- Other

P (<15y):

Body weight	Intensive phase (2HRZES* + 1HRZE) (No. of tablets)		Continuation phase (5HRE)
	HRZ	E (100 mg)	HRE+
4-7 kg	1	1	1
8-11 kg	2	2	2
12-15 kg	3	3	3
16-24 kg	4	4	4
25+ kg	Adult dose and preparations		

*Add streptomycin 15 mg/kg BW/d during the first 2 months of the intensive phase, not to exceed 1 g/d.

All retreatment patients are considered as Presumptive DR-TB and should therefore be tested using Xpert MTB/Rif Test **before initiating** Category II treatment regimen (except if there is no sputum specimen, or there is no access to Xpert services).

Category II regimen should only be given among SUSCEPTIBLE retreatment cases. They should immediately be referred to the nearest MDR-TB facility (or other private or government facility with Xpert/MTB/Rif service) for Rifampicin susceptibility testing (Xpert).

For patients with BW <50 kgs and those >60 yrs old, consider streptomycin dosing of 500-700mg or 10mg/kg/d.

A:

Body weight	Intensive phase (2HRZES* + 1HRZE) (No. of tablets)		Continuation phase (5HRE)
	HRZES*	HRZE	HRE
30-37 kg	2	2	2
38-54 kg	3	3	3
55-70 kg	4	4	4
>70 kg	5	5	5

*Add streptomycin 15 mg/kg BW/d during the first 2 months of the intensive phase, not to exceed 1 g/d.

Xpert MTB/Rif test shall be done first and result be made available before starting on any second-line drugs.

Category IIa
2HRZES/1HRZE/9HRE

EPTB, previously treated drug-susceptible TB (whether bacteriologically-confirmed or clinically-diagnosed) - CNS, bones or joints

P (<15y):

Body weight	Intensive phase (2HRZES* + 1HRZE) (No. of tablets)		Continuation phase (9HRE)
	HRZ	E (100 mg)	HRE+
4-7 kg	1	1	1
8-11 kg	2	2	2
12-15 kg	3	3	3
16-24 kg	4	4	4
25+ kg	Adult dose and preparations		

*Add streptomycin 30 mg/kg BW/d during the first 2 months of the intensive phase, not to exceed 1 g/d.

Pre-treatment recommendations for patients starting Category II regimens:

1. Baseline history and PE for any risk factors for hepatic, renal and ocular toxicity; sexual history; occupational history; personal/ social personal (including smoking and alcohol use)
2. Those with risk behavior for HIV or coming from Category A/B HIV areas should be offered PICT
3. Baseline ALT/crea at the minimum for >60y/o and those with risk factors for liver or kidney disease
4. Screening for DM (using FBS, RBS or OGTT) for all TB patients
5. Baseline visual acuity and color perception for all TB patients

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<u>A:</u>
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<tr><th rowspan="2">Body weight</th><th colspan="2">Intensive phase (2HRZES* + 1HRZE) (No. of tablets)</th><th>Continuation phase (9HRE)</th></tr>
<tr><th>HRZES*</th><th>HRZE</th><th>HRE</th></tr>
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<tr><td>>70 kg</td><td>5</td><td>5</td><td>5</td></tr>
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*Add streptomycin 30 mg/kg BW/d during the first 2 months of the intensive phase, not to exceed 1 g/d.
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<td>Standard Regimen Drug-resistant (SRDR)

Rifampicin-resistant TB or Multidrug-resistant TB (MDR-TB)</td>
<td>Shorter Treatment Regimen:
Moxifloxacin-Kanamycin-Prothionamide-Clofazimine-Pyrazinamide-Ethambutol-Isoniazid high dose (MfxKmPtoCfzEZH)
• Strictly provided to MDR/RR-TB only.
• Treatment duration for 9-11 months.</td>
<td>Since second-line drugs (SLDs) come in single dose formulations, DOT shall be done throughout the treatment duration to ensure adherence.

Refer to the treatment centers/ satellite treatment centers for DR-TB management.</td>
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	Conventional Treatment Regimens • Provided to patients who do not qualify for the Shorter Treatment Regimen. • Treatment duration for 20-24 months.	
XDR-TB Regimen	Treatment shall be individualized based on DST result and history of previous treatment and managed only by PMDT center.	

Individual Condition/ Special Situations	Preferred regimen	Comments
People living with Human immunodeficiency Virus (HIV)	In HIV-related TB, the priority is to treat TB. Standard TB regimen for HIV-associated TB is the same as the general population. ARV should be initiated after the 2nd week of TB treatment. For patients with TB meningitis, ARV should be given after the Intensive Phase of TB treatment. Cotrimoxazole prophylaxis (sulfamathoxazole 800mg/ trimethoprim 160 mg daily) for *Pneumocystis jiroveci* pneumonia regardless of CD4 count.	All newly diagnosed PLHIV should be screened for active TB. All PLHIV with cough of any duration, fever, night sweats, or loss of weight shall undergo sputum collection for Xpert testing. PLHIV without these symptoms should undergo chest x-ray or clinical assessment to rule out EPTB. Should there be cutaneous reactions observed in HIV-infected individuals, it is important to note that RIF should be re-introduced last. Efavirenz is the preferred NNRTI for PLHIV on TB treatment. Avoid the use of nevirapine because of drug-drug interactions. Pyridoxine (Vitamin B6) at 10-25 mg/d.
Diabetes Mellitus	Same as general population	Glucose control should be optimal, referral to specialist is recommended for difficult to control diabetes
New Miliary TB and Miliary TB with dissemination	Treat as Category I: 2HRZE/4HR	In the absence of meningitis or bone and joint involvement, the effective treatment regimen for NEW miliary TB cases is Category I.
Pregnancy	Standard TB regimen for pregnant is the same as the general population. Pregnant patients taking Isoniazid should be given Pyridoxine (Vitamin B6) at 10-25 mg/d.	Always ascertain whether or not a woman is pregnant before she starts TB treatment. First line anti-TB drugs are safe for pregnant women, EXCEPT streptomycin (an ABSOLUTE contraindication).

Breastfeeding/Lactating women	Standard TB regimen for breastfeeding/Lactating women is the same as the general population. Breastfeeding/Lactating women should be given Pyridoxine (Vitamin B6) at 10-25mg/d. Supplemental Pyridoxine should be given at 5-10 mg/d to the infant who is taking isoniazid or whose breastfeeding mother is taking isoniazid.	Breastfeeding woman afflicted with TB should receive a full course of TB treatment. In lactating mothers on TB treatment, most anti-TB drugs will be found in breast milk in concentrations equal to only a small fraction of the therapeutic dose in infants.
Oral Contraceptives	Category I: Category I: 2HRZE/4HR	Rifampicin interacts with oral contraceptive (OC) medications with a risk of decreased protective efficacy against pregnancy. Advise a woman receiving OC while on Rif treatment that she has the following options: 1) Take an OC pill containing a higher dose of estrogen (50 u) following consultation with a clinician 2) Use another form of contraception
Liver Disease / History of Liver disease	Treatment should be interrupted and generally modified or alternative regimen used for those with alanine aminotransferase (ALT) elevation >3x the upper limit of normal (ULN) in the presence of hepatitis symptoms/or jaundice. If ALT is elevated 5x the ULN, treatment should be interrupted even in the absence of symptoms. **Refer to the appropriate specialist.**	

Chronic Liver Disease	For compensated liver cirrhosis: 2HRSE/6HR 2HSE/10HE 9HRE	Patients undergoing prolonged ethambutol treatment should undergo regular ophthalmologic screening (visual acuity and red/green color discrimination). For decompensated liver cirrhosis: Refer to a specialist because use of possible SLDs is warranted. The more advanced the liver disease, the fewer number of hepatotoxic drugs should be used.
Acute Viral Hepatitis	It is possible to defer TB treatment until acute hepatitis has been resolved. When it is necessary to treat TB during acute hepatitis, the safest option is the combination of streptomycin and ethambutol for 3 months. Once the hepatitis has resolved, a Continuation Phase of 6 months HR is given (3SE/6HR). If the hepatitis has not been resolved, SE should be continued for a total of 12 months (12SE). Refer all patients to a specialist.	
Known Chronic Kidney Disease	2HRZE/4HR modified in dosage and frequency based on creatinine clearance Thrice weekly instead of daily pyrazinamide and ethambutol is recommended.	Please refer to the Table below on Dose Adjustments for Patients with Kidney Disease. Anti-TB medications should be administered immediately AFTER hemodialysis or ANYTIME during peritoneal dialysis.

		SDFs are preferred over FDCs to facilitate proper dose adjustments. Same adjustments are made for those receiving second line drugs.
Renal Failure (with reduced renal function or receiving hemodialysis)	H: 300 mg od; or 900 mg 3x per week R: 600 mg od; or 600 mg 3x per week Z: 25-35 mg/kg/dose 3x per week (NOT daily) E: 15-25 mg/kg/dose 3x per week (NOT daily) S: 12-15 mg/kg/dose 2 or 3x per week	Noting the recommendations cited, it is possible to give a 4-drug FDC (HRZE) 3x per week and then give a 2-drug FDC (HR) for the rest of the week during the Intensive Phase. Continuation Phase may proceed with 4HR. Otherwise, another safe option is 2HRZ/4HR. It is recommended that anti-TB medications be taken after hemodialysis.

Summary of treatment regimens for Extra-pulmonary TB

Site	Regimen	Recommendation/ Level of Evidence
Central Nervous System	2 HRZE / 10 HR	STRONG recommendation, High quality evidence
Bone and Joints	2 HRZE / 10 HR	STRONG recommendation, Moderate quality evidence
Lymph node	2 HRZE / 4 HR	STRONG recommendation, Moderate quality evidence
Pericardium	2 HRZE / 4 HR	STRONG recommendation, Low quality evidence
Pleura	2 HRZE / 4 HR	STRONG recommendation, Moderate quality evidence
Liver	2 HRZE / 4 HR	STRONG recommendation, Moderate quality evidence
Gastrointestinal, Peritoneum	2 HRZE / 4 HR	STRONG recommendation, Moderate quality evidence
Kidney and Genitourinary tract	2 HRZE / 4 HR	STRONG recommendation, Low quality evidence

Dose Adjustments for Patients with Kidney Disease

Anti-TB drug	Reference dose (normal renal function)	Dose adjustment			
		GFR ≥ 30 ml/min	GFR < 30 ml/min	Hemodialysis	Peritoneal dialysis
Isoniazid	5 (4-6) mg/kg/d (max 300 mg/d)	None		After dialysis	None
Rifampicin	10 (8-12) mg/kg/d (max 600 mg/d)	None		After dialysis	None
Pyrazinamide	25 (20-30) mg/kg/d (max 2 g/d)	None	25-35 mg/kg, 3x/week	25-35 mg/kg, 3x/week, after dialysis	25-35 mg/kg, 3x/week
Ethambutol	15 (15-20) mg/kg/d (max 1.2 g/d)	GFR ≥ 70 ml/min: None GFR < 70 ml/min: 15-25 mg/kg, 3x/week	15-25 mg/kg, 3x/week	15-25 mg/kg, 3x/week, after dialysis	15-25 mg/kg, 3x/week

References:

1. WHO Treatment of Tuberculosis Guidelines, 4th edition. Geneva, Switzerland: WHO, 2010.
2. National Tuberculosis Control Program Manual of Procedures, 5th edition. Sta. Cruz, Manila: DOH, 2014.
3. CPG for the Diagnosis, Treatment, Prevention and Control of Tuberculosis in Adult Filipinos – 2016 Update. Manila: Philippine Coalition Against Tuberculosis (PhilCAT); 2016.