TABLE 205e-2 SIMPLIFIED APPROACH TO TREATMENT OF ACTIVE TUBERCULOSIS (TB) IN ADULTS

Culture Results	Intensive Phase	Continuation Phase	Extension of Total Treatment
Culture positive	HRZE for 2 months, daily or intermittent (with dose adjustment)	HR for 4 months, daily or 5 d/wk *or* HR for 4 months, intermittent (with dose adjustment)	To 9 months, if 2 months of Z is not completed or culture conversion is prolonged and cavitation is evident on plain radiograph[a]
Culture negative	HRZE for 2 months	2 months	To 6 months, if patient is infected with HIV
Extrapulmonary	HRZE for 2 months	HR for 4–7 months, daily or 5 d/wk[b]	To 9–12 months in TB meningitis. Some recommend 9 months for bone/joint TB.
Resistant to H	QRZE[c] or, less often, RZES for 6 months	…	Prolonged culture conversion, cavitation
Resistant to R	HZEQ[c] (IA[d]) for 2 months	HEQ(S) for 10–16 months	Prolonged culture conversion, delayed response
Resistant to HR[e]	ZEQ[c] (IA[d]) ± alternative agents[f] for 18–24 months	…	Prolonged culture conversion

[a]Culture conversion is prolonged if it occurs beyond 2 months. Some providers extend the continuation phase to 7 months if there is *either* prolonged culture conversion or cavitation. [b]Many experts recommend a continuation phase of 7 months for all extrapulmonary TB, including miliary disease. For TB pericarditis and meningitis, the addition of glucocorticoids is recommended. [c]Levofloxacin and moxifloxacin are the preferred fluoroquinolones. Gatifloxacin is associated with dysglycemia but may be an acceptable alternative; in a recent trial of TB treatment, this drug did not cause dysglycemia in patients who received it thrice weekly for 4 months. Ofloxacin and ciprofloxacin should generally be avoided because of resistance. [d]Injectable agents: streptomycin, amikacin, kanamycin, and capreomycin. [e]Multidrug-resistant TB should be managed by or in close consultation with an expert TB clinician. Surgical management should be considered. [f]Alternative agents: cycloserine, ethionamide, para-aminosalicylic acid, clarithromycin, linezolid, and amoxicillin-clavulanate.

Abbreviations: E, ethambutol; H, isoniazid; IA, injectable agent; Q, fluoroquinolone; R, rifampin; S, streptomycin; Z, pyrazinamide.

Sources: American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Am J Respir Crit Care Med 167:603, 2003; C Mitnick et al: N Engl J Med 359:563, 2008; World Health Organization 2011 update: Guidelines for the programmatic management of drug-resistant tuberculosis (*www.who.int/tb/challenges/mdr/programmatic_guidelines_for_mdrtb/en/index.html*).

on the basis of complete phenotypic and, if possible, genotypic antimicrobial susceptibility testing. Therapeutic regimens for either MDR-TB or XDR-TB should be constructed with input from experienced clinicians who should continue the management of the disease.

FIRST-LINE ANTITUBERCULOSIS DRUGS

The following discussion of individual anti-TB agents focuses on treatment of TB in adults, unless otherwise noted. Several agents are being actively investigated during the current remarkable period of drug development for TB treatment.

Isoniazid Isoniazid is a critical drug for treatment of both TB disease and LTBI. Isoniazid has excellent bactericidal activity against both intracellular *M. tuberculosis* and extracellular, actively dividing organisms. This drug is bacteriostatic against slowly dividing organisms. In treatment of LTBI, isoniazid is considered the first-line agent because it is generally well tolerated, has well-established efficacy, and

TABLE 205e-3 MONITORING AND CLINICAL MANAGEMENT OF TUBERCULOSIS TREATMENT IN ADULTS[a]

Drug	Assessment	Management
LTBI Treatment		
With hepatic risk factors[b], check ALT and bilirubin at baseline. If ALT is ≥3 × ULN or total bilirubin is >2 × ULN, defer treatment and reevaluate.		
Isoniazid	Determine whether hepatic risk factors are present. If so, obtain baseline and periodic ALT and bilirubin values.	If ALT is 5 × ULN (or 3 × ULN with symptoms)[c] or if bilirubin reaches jaundice levels (usually >2 × ULN), interrupt treatment. With normalization, consider an alternative agent.
Rifampin	Same as above	Same as above
TB Treatment		
Check ALT, bilirubin, platelets, creatinine, and hepatitis panel for all patients at baseline. If hepatic risk factors are present, check ALT and bilirubin monthly.		
Isoniazid	If ALT is >5 × ULN (or >3 × ULN with hepatitis symptoms)[c]	Obtain history of alcohol consumption and concomitant drug use. In most instances, discontinue isoniazid, pyrazinamide, rifampin, and other hepatotoxic drugs. Consider alternative agents. Obtain viral hepatitis serologies. Rechallenge: With normalization of liver enzymes, rifampin and isoniazid may be sequentially reintroduced. With no recurrence of hepatotoxicity, pyrazinamide is not resumed in many cases. Alternative rechallenge protocols have been used.
Rifampin	If primary elevation is in bilirubin and alkaline phosphatase, most likely due to rifampin	Discontinue rifampin if total bilirubin reaches jaundice levels (usually >2 × ULN). May try to reintroduce; if not tolerated, may substitute fluoroquinolone
Ethambutol	Decrease in visual acuity or color vision or appearance on monthly screening	Discontinue ethambutol and repeat ocular exam. Peripheral neuropathy may be a precursor of ocular toxicity; if it occurs, consider repeat ocular exam.
Pyrazinamide	If ALT is >5 × ULN (or >3 × ULN with symptoms)[c]	Same as for isoniazid
Fluoroquinolone	If QTc prolongation is discovered incidentally on ECG	Check audiometry and at least BUN and creatinine monthly.
Aminoglycoside	Abnormal results on audiometry testing, BUN, creatinine, electrolytes at baseline or on monthly check	Discontinue aminoglycoside if not MDR-TB. As appropriate, assess renal function, correct electrolytes, or seek ENT consultation.

[a]All regimens require monthly clinical monitoring. [b]Hepatic risk factors: chronic alcohol use, viral hepatitis, preexisting liver disease, pregnancy or ≤3 months postpartum, hepatotoxic medications. [c]Relevant manifestations include nausea, vomiting, abdominal pain, jaundice, or unexplained fatigue.

Abbreviations: ALT, alanine aminotransferase; BUN, blood urea nitrogen; ECG, electrocardiogram; ENT, ear, nose, and throat; LTBI, latent tuberculosis infection; MDR-TB, multidrug-resistant tuberculosis; ULN, upper limit of normal.

Sources: JJ Saukkonen et al: Am J Respir Crit Care Med 174:935, 2006; American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Am J Respir Crit Care Med 167:603, 2003.