

Antimycobacterial Agents

Chapter 186 | Part 5: Infectious Diseases

KEY CLINICAL POINTS

- 1 TB treatment requires multi-drug regimens to prevent resistance; standard intensive phase is 2 months (HRZE) followed by a continuation phase (HR).
- 2 Latent TB Infection (LTBI) regimens include Isoniazid plus Rifapentine (3 months weekly), Rifampin (4 months daily), or Isoniazid (6-9 months).
- 3 MDR-TB is defined by resistance to both Isoniazid and Rifampin; new WHO guidelines recommend all-oral bedaquiline-containing regimens (e.g., BPaLM) for 6 months.
- 4 Isoniazid toxicity includes hepatotoxicity (discontinue if ALT >5x ULN or >3x ULN with symptoms) and peripheral neuropathy (prevent with pyridoxine).
- 5 Rifampin is a potent CYP450 inducer causing drug interactions (e.g., warfarin, protease inhibitors); it turns body fluids orange-red.
- 6 HIV co-infection requires careful ART timing (within 2 weeks if CD4 ≤50/μL) and monitoring for Immune Reconstitution Inflammatory Syndrome (IRIS).
- 7 NTM treatment depends on species (MAC, *M. kansasii*, *M. abscessus*, *M. marinum*) and susceptibility; *M. abscessus* is difficult to cure and often requires surgical resection.
- 8 Drug resistance mechanisms include *katG*/*inhA* mutations (isoniazid), *pncA* mutations (pyrazinamide), *rpoB* mutations (rifampin), and efflux pump upregulation (*efpA*, *mmpL7*).
- 9 Monitoring includes monthly clinical assessment, liver function tests (ALT, bilirubin), and specific toxicity checks (visual acuity for ethambutol, QTc for fluoroquinolones/bedaquiline).
- 10 Treatment adherence is critical; strategies include Directly Observed Therapy (DOT), mobile health technologies, and monthly dispensing.

1. DEFINITION & OVERVIEW

Antimycobacterial agents are used for treating mycobacterial infections, including tuberculosis (TB), leprosy, and nontuberculous mycobacteria (NTM). These infections require multi-drug regimens for prolonged courses.

Definition (Harrison's 22e): *<i>Tuberculosis is a chronic infectious disease caused by Mycobacterium tuberculosis, characterized by granulomatous inflammation and progressive tissue destruction.</i>*

Key considerations:

- **Scope:** >180 mycobacterial species exist, but most do not cause human disease.
- **Trends:** TB incidence has declined globally but increased during the COVID-19 pandemic.
- **Impact:** TB remains a leading cause of mortality in low- and middle-income countries, especially sub-Saharan Africa with high TB/HIV co-infection rates.

- **NTM Status:** NTM infections are increasingly recognized in developed countries, often affecting immunocompromised individuals or those with structural lung disease.
- **LTBI Diagnosis:** Diagnosed via history, imaging, skin tests, interferon- γ release assays, and molecular diagnostics.
- **Active TB Confirmation:** Requires culture/molecular testing for confirmation.

1.1 Global Considerations

- **Diagnosis:** Pulmonary TB is often diagnosed by smear microscopy in many countries.
- **NTM Identification:** NTM may be misidentified as relapsed TB in some cases.
- **Prognosis of Misidentification:** As TB incidence declines, the proportion of NTM isolates among positive smears will increase. Specialized diagnostics are needed to distinguish TB from NTM infections.

1.2 Nontuberculous Mycobacteria (NTM)

- **Definition:** Environmental organisms that cause disease in immunocompromised patients or those with structural lung disease.
- **Treatment Strategy:** Varies by species; macrolides and aminoglycosides are typically effective, but expert consultation is recommended for complex cases.

2. EPIDEMIOLOGY

Global TB incidence has declined but increased during the pandemic. TB remains a major cause of morbidity/mortality in low- and middle-income countries.

NTM infections are increasing in developed nations, disproportionately affecting immunocompromised individuals or those with structural lung disease.

2.1 TB/HIV Co-infection

- **Prevalence:** High prevalence in sub-Saharan Africa.
- **Control Requirements:** Requires infrastructure for early diagnosis, treatment, and vaccine development.

2.2 NTM Epidemiology

- **Demographics:** Increasingly recognized in developed countries; affects immunocompromised individuals or those with structural lung disease.

3. ETIOLOGY & PATHOPHYSIOLOGY

M. tuberculosis is the primary TB pathogen. NTM species include *MAC*, *M. kansasii*, *M. abscessus*, and *M. marinum*.

Resistance Mechanisms:

- **Isoniazid:** 70-80% due to *katG* or *inhA* mutations; 20-30% due to efflux pump upregulation (*efpA*, *mmpL7*); also via NADH dehydrogenase 2 loss.
- **Pyrazinamide:** 72-98% of resistant isolates have *pncA* mutations.
- **Rifampin:** Rare monoresistance; treated as MDR-TB.

Definition (Harrison's 22e): *<i>Immune Reconstitution Inflammatory Syndrome (IRIS) is a paradoxical worsening of TB symptoms following initiation of ART in HIV-positive patients.</i>*

IRIS Management:

- **Timing:** Typically occurs within 1 week of ART.
- **Action:** Requires exclusion diagnosis; continue ART/TB drugs; use glucocorticoids for severe cases.

3.1 Resistance Mechanisms

- **Isoniazid:**
 - 70-80% katG or inhA mutations
 - 20-30% efflux pump upregulation (efpA, mmpL7)
 - NADH dehydrogenase 2 loss
- **Pyrazinamide:** 72-98% pncA mutations
- **Rifampin:** Rare monoresistance; treated as MDR-TB

3.2 IRIS Pathophysiology

- **Timing:** Occurs within 1 week of ART initiation in HIV/TB co-infected patients.
- **Management:** Continue ART and TB drugs; glucocorticoids for severe cases.
- **Evidence:** Randomized trial showed prednisone reduced hospitalization needs and improved quality of life in TB IRIS.

4. CLINICAL FEATURES

TB presents with persistent cough, fever, anorexia, and severe lung destruction. Symptoms worsen without treatment but improve with therapy.

NTM shares similar clinical features but may require prolonged treatment when sputum remains positive.

Drug Toxicity Manifestations:

- **Hepatotoxicity:** Jaundice, dark urine, pruritus, nausea, vomiting.
- **Peripheral Neuropathy:** Numbness, tingling.
- **Optic Neuritis:** Visual acuity loss.
- **QTc Prolongation:** Palpitations.
- **Bone Marrow Suppression:** Anemia, thrombocytopenia, leukopenia.

4.1 TB Clinical Features

- **Presentation:** Persistent cough, fever, anorexia, and severe lung destruction; symptoms worsen without treatment but improve with therapy.

4.2 NTM Clinical Features

- **Presentation:** Persistent cough, fever, anorexia, and severe lung destruction; treatment may need prolongation if sputum remains positive.

4.3 Drug Toxicity

- **Hepatotoxicity:** Nausea, vomiting, jaundice

- **Peripheral Neuropathy:** Numbness, tingling
 - **Optic Neuritis:** Visual acuity loss
 - **QTc Prolongation:** Palpitations
 - **Bone Marrow Suppression:** Anemia, thrombocytopenia, leukopenia
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5. DIFFERENTIAL DIAGNOSIS

Distinguish TB from NTM using specialized diagnostics. MDR-TB is defined as resistance to both isoniazid and rifampin.

IRIS is a diagnosis of exclusion in HIV/TB co-infected patients.

5.1 MDR-TB Definition

Definition (Harrison's 22e): *Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to at least isoniazid and rifampin, the two most effective first-line drugs.*

- **Risk Factors:** Patients from regions with $\geq 5\%$ MDR-TB incidence or prior TB treatment.

5.2 IRIS Diagnosis

Definition (Harrison's 22e): *Immune Reconstitution Inflammatory Syndrome (IRIS) is a paradoxical worsening of TB symptoms following initiation of ART in HIV-positive patients.*

- **Requirement:** Diagnosis requires exclusion of other causes and confirmation of HIV/TB co-infection.
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6. INVESTIGATIONS & DIAGNOSIS

LTBI is diagnosed via history, imaging, skin tests, interferon- γ release assays, and molecular diagnostics.

Active TB requires culture/molecular testing for *M. tuberculosis* confirmation.

Monitoring includes monthly clinical assessment, liver function tests (ALT, bilirubin), and specific toxicity checks.

6.1 LTBI Diagnosis

Diagnostic methods:

- History and physical examination
- Radiographic imaging
- Tuberculin skin test
- Interferon- γ release assays
- Acid-fast staining
- Mycobacterial cultures
- Molecular diagnostics

6.2 Active TB Diagnosis

Confirm via culture/molecular testing.

- **Clinical Guidance:** Clinical factors (HIV status, symptom duration, radiographic findings) guide diagnostic testing and treatment initiation.

6.3 Monitoring

Monitoring protocols:

- Monthly clinical assessment for hepatotoxicity symptoms
- Baseline liver function tests (ALT, bilirubin)
- Monthly sputum cultures until clearance
- Visual acuity screening for ethambutol
- QTc monitoring for fluoroquinolones/bedaquiline

7. MANAGEMENT & TREATMENT

Active TB treatment requires standardized regimens with intensive (HRZE) and continuation (HR) phases. U.S. guidelines recommend extending continuation phase to 7 months for cavitary disease or delayed culture conversion.

New WHO recommendations: All-oral bedaquiline-containing regimens (e.g., BPaLM) for 6 months in MDR-TB.

HIV/TB co-infection management:

- Initiate ART within 2 weeks if CD4 $\leq 50/\mu\text{L}$, or 8-12 weeks if CD4 $\geq 50/\mu\text{L}$
- Rifabutin is preferred over rifampin in HIV patients due to lower CYP3A inhibition.
- Rifampin interacts with protease inhibitors/nonnucleoside reverse transcriptase inhibitors; requires monitoring and dose adjustments.
- Intermittent therapy not recommended for HIV/TB co-infected individuals.

7.1 LTBI Treatment

Regimens (Reference Table 186-1):

- **Isoniazid plus rifapentine:** 900 mg (15 mg/kg) weekly + 900 mg (for weight > 50 kg) weekly; 3 months. (DOT recommended for all; add pyridoxine 25-50 mg/d).
- **Rifampin:** 600 mg/d (10 mg/kg); 4 months. (Recommended in HIV-negative and children).
- **Isoniazid plus rifampin:** 300 mg/d (5 mg/kg) + 600 mg/d (10 mg/kg); 3 months. (Higher hepatotoxicity risk).
- **Isoniazid:** 300 mg/d (5 mg/kg) or 900 mg twice weekly (15 mg/kg); 6-9 months.

Note: 3-month regimen preferred for children > 2 years and adults, including HIV-positive. Avoid in pregnancy/hypersensitivity cases.

7.2 Active TB Treatment

Standard regimen: HRZE (2 months) + HR (4 months).

- **Cavitary/Delayed Conversion:** Extend continuation phase to 7 months (U.S. guidelines).
- **MDR-TB:** Use BPaLM or other all-oral bedaquiline regimens for 6 months.

7.3 MDR-TB Treatment

Treatment regimens (Reference Table 186-4):

- **Resistant to H:** Lfx RZE for 6 months; OR Bdq, Pa, Lz, Mfx for 6 months (may drop Mfx if documented Q resistance).
- **Resistant to HR (MDR):** Bdq plus Lfx or Mfx, Eto, E, Z, Hh, Cfz for 4-6 months; then Lfx or Mfx, Cfz, Z, E for 5 months.
- **WHO Short-course:** Bdq plus Lfx or Mfx, Eto, E, Z, Hh, Cfz for 4-6 months; then Lfx or Mfx, Cfz, Z, E for 5 months (18-20 months total or 15-17 months after culture conversion).

7.4 HIV Co-infection Management

- **ART Timing:** <2 weeks if CD4 $\leq$ 50/ μ L; 8-12 weeks if CD4 $\geq$ 50/ μ L.
- **Drug Choice:** Rifabutin preferred over rifampin due to lower CYP3A inhibition.
- **Interactions:** Rifampin with protease inhibitors/nonnucleoside reverse transcriptase inhibitors requires monitoring and dose adjustments.

7.5 Adherence Strategies

Critical strategies:

- Directly Observed Therapy (DOT) by trained staff
- Mobile health technologies (video DOT, text messaging)
- Monthly dispensing of medications for monitoring hepatotoxicity
- Patient education/counseling and home visits

8. PROGNOSIS & COMPLICATIONS

NTM prognosis varies by species; *M. abscessus* is particularly challenging to treat and may require surgical resection.

Treatment failure risks:

- Incomplete adherence
- Poor medication absorption
- Development of resistance

IRIS requires careful monitoring and management with glucocorticoids in severe cases.

8.1 NTM Prognosis

Prognosis depends on species:

- **MAC:** Better outcomes with macrolides/aminoglycosides.
- **M. abscessus:** Poor prognosis; often requires surgery.
- **M. kansasii:** Chronic disease requiring prolonged treatment.

8.2 Treatment Failure

Common causes:

- Non-adherence to medication regimens
- Drug resistance development
- Poor absorption of medications

Management requires drug susceptibility testing and addition of alternative agents.

9. SPECIAL CONSIDERATIONS

Pregnancy: 3-month regimen contraindicated; Isoniazid monotherapy (6-9 months) preferred for LTBI.

Liver disease: Monitor ALT/bilirubin monthly; discontinue hepatotoxic agents if thresholds exceeded.

HIV co-infection: Initiate ART within 2 weeks if CD4 $\leq 50/\mu\text{L}$; use rifabutin instead of rifampin.

9.1 Pregnancy

Avoid 3-month Isoniazid/rifapentine regimen; use Isoniazid monotherapy (6-9 months) for LTBI.

9.2 Liver Disease

Monitor ALT/bilirubin monthly; discontinue if thresholds exceeded.

9.3 HIV Co-infection

ART timing: < 2 weeks if CD4 $\leq 50/\mu\text{L}$; use rifabutin instead of rifampin due to lower CYP3A inhibition.

KEY PEARLS & HIGH-YIELD POINTS

- **MDR-TB:** Requires all-oral regimens with bedaquiline/pretomanid.
- **IRIS:** Diagnosis of exclusion in HIV/TB co-infected patients.
- **Rifampin:** Causes orange-red body fluids; potent CYP450 inducer.
- **Isoniazid:** Pyridoxine prevents induced peripheral neuropathy.
- **Adherence:** Monthly dispensing improves adherence and monitoring.

Clinical Traps:

- Overlooking NTM in smear-positive cases.
- Using intermittent therapy in HIV/TB co-infected patients.
- Delaying ART initiation in HIV/TB co-infection.

REFERENCE TABLES

TABLE 186-1

Regimens for the Treatment of Latent Tuberculosis Infection in Adults REGIMEN Isoniazid plus rifapentine Rifampin...

REGIMEN	SCHEDULE	DURATION	COMMENTS
Isoniazid plus rifapentine	900 mg (15 mg/kg) weekly plus 900 mg (for weight > 50 kg) weekly	3 months	Directly observed therapy is recommended for once-weekly treatment in HIV-positive and -negative individuals. This regimen may be supplemented with pyridoxine (25–50 mg/d).

REGIMEN	SCHEDULE	DURATION	COMMENTS
	600 mg/d (10 mg/kg)	4 months	
Isoniazid plus rifampin	300 mg/d (5 mg/kg) plus 600 mg/d (10 mg/kg)	3 months	Risk of hepatotoxicity may be higher with the combination regimen compared to that of the individual drugs.
	300 mg/d (5 mg/kg) Alternative: 900 mg twice weekly (15 mg/kg)	6–9 months (6 months acceptable)	

TABLE 186-2

Simplified Approach to Treatment of Active Tuberculosis (TB) in Adults

CULTURE RESULTS	INTENSIVE PHASE	CONTINUATION PHASE	EXTENSION OF TOTAL TREATMENT
Culture-positive, drug-susceptible	HRZE for 2 months, daily ^a or 3 times per week (with dose adjustment)	HR for 4 months, daily or 5 days per week or HR for 4 months, 3 times per week ^b (with dose adjustment)	Continuation phase extended to 7 months if 2 months of Z is not completed, if the patient is infected with HIV and is not receiving antiretroviral therapy, or if culture conversion is prolonged and/or cavitation is evident on chest radiography (U.S. guidelines) ^c
	HRZE for 2 months	HR for 2 months, daily or 2 or 3 times per week ^d	
Extrapulmonary, drug-susceptible	HRZE for 2 months	HR for 4–7 months, daily or 5 days per week ^e	Continuation phase extended to 10 months in TB meningitis; 7 months recommended by some authorities for bone/joint TB

TABLE 186-3

Monitoring and Clinical Management of Tuberculosis (TB) Treatment in Adults ^a

DRUG	ASSESSMENT	MANAGEMENT
LTBI Treatment		
	With hepatic risk factors ^b , check ALT and bilirubin at baseline. If ALT is $\geq 3 \times$ ULN or total bilirubin is $> 2 \times$ ULN, defer treatment and reevaluate.	

DRUG	ASSESSMENT	MANAGEMENT
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		
If ALT is >5× ULN (or >3× ULN with hepatitis symptoms)c		
If primary elevation is in bilirubin and alkaline phosphatase, most likely due to rifampin		
Decrease in visual acuity or color vision on monthly screening		
If ALT is >5× ULN (or >3× ULN with symptoms)c		
QTc prolongation is a concern and should be monitored, especially if drugs are used in combination		
Visual impairment; monitor for peripheral neuropathy and bone marrow suppression including anemia, thrombocytopenia, and leukopenia		

TABLE 186-4
Simplified Approach to Treatment of Drug-Resistant Tuberculosis (TB) in Adults a

CULTURE RESULTS	INTENSIVE PHASE	CONTINUATION PHASE	EXTENSION OF TOTAL TREATMENT
Resistant to H	Lfx RZEb for 6 months	...	Prolonged culture conversion and/or evidence of cavitation on chest radiography.

CULTURE RESULTS	INTENSIVE PHASE	CONTINUATION PHASE	EXTENSION OF TOTAL TREATMENT
	Bdq, Pa, Lz, Mfx for 6 months (may drop Mfx if documented Q resistance) Bdq plus Lfx or Mfx, Eto, E, Z, Hh, Cfz for 4–6 months At least four effective second-line agents, including all three group A and at least one group B; add group C if intolerant to A or B drugs for 5–7 months	Lfx or Mfx, Cfz, Z, E for 5 months At least 4 drugs for a total of 18–20 months or for 15–17 months after culture conversion	