

Antimycobacterials

The RIPE combination (rifampin, isoniazid, pyrazinamide, ethambutol) that anchors first-line tuberculosis treatment, plus the second-line and antileprosy agents used when resistance, intolerance or a different mycobacterium changes the picture.

Online guide: <https://www.medguideglobal.com/pharmacology/antivirals-antifungals-antiparasitics/antimycobacterials>

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Quick revision

One Liner: Four first-line drugs - rifampin, isoniazid, pyrazinamide and ethambutol (RIPE) - are combined for the first two months of standard tuberculosis treatment specifically because combination therapy, not any single agent, is what prevents acquired drug resistance.

1. Isoniazid is a prodrug activated by the mycobacterial catalase-peroxidase KatG; its active metabolite blocks mycolic acid synthesis, the building block of the mycobacterial cell wall. [7]
2. Rifampin inhibits DNA-dependent RNA polymerase in Mycobacterium tuberculosis, blocking bacterial transcription, and separately induces a broad panel of cytochrome P450 enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4) that lowers the levels of many co-administered drugs. [2]
3. Pyrazinamide's own mechanism is stated as unknown on its FDA label, but it requires the acidic pH found inside the macrophage phagolysosome to work, which is why it is most useful early in treatment against semi-dormant intracellular organisms. [3]
4. Ethambutol is the drug of the group that carries dose-related optic neuritis as its defining toxicity, monitored by baseline and periodic visual acuity and colour vision testing. [4]
5. All four first-line agents can be hepatotoxic; isoniazid's hepatitis risk and its dose-related peripheral neuropathy (managed with pyridoxine/vitamin B6 in patients at risk) are the two toxicities most tied to this specific drug on exam. [1]
6. Rifampin turns body fluids - urine, sweat, tears, saliva - an orange-red colour, a harmless but clinically important counselling point that also warns a patient the drug is being absorbed. [2]
7. Bedaquiline is reserved for pulmonary tuberculosis resistant to at least rifampin and isoniazid (multidrug-resistant TB) and is always given with at least three other active drugs, never as monotherapy, because of QTc-prolongation risk requiring ECG monitoring. [5]
8. Leprosy (Hansen disease) uses a separate three-drug WHO multidrug therapy regimen - dapsone, rifampin and clofazimine - rather than the RIPE combination used for tuberculosis. [8]

Overview

1. Antimycobacterial drugs treat infections by two very different-behaving members of the genus Mycobacterium: Mycobacterium tuberculosis, the cause of tuberculosis, and Mycobacterium leprae, the cause of leprosy. Both organisms share a thick, lipid-rich cell wall that limits which drugs can even reach an intracellular target, and both are treated with multidrug combinations for the same underlying reason - a single agent used alone lets the small fraction of naturally resistant organisms in a large bacterial population survive and repopulate the infection. [7]
2. The tuberculosis regimen that anchors first-line treatment is built from four drugs given together, commonly abbreviated RIPE: rifampin, isoniazid, pyrazinamide and ethambutol. The WHO's consolidated guidelines describe the standard drug-susceptible regimen as an intensive phase combining all four drugs, followed by a continuation phase of rifampin and isoniazid alone once the more actively multiplying organisms have been substantially reduced. Newer WHO-recommended shorter regimens exist for specific populations, but the four-drug intensive phase remains the reference point most exam questions are built around. [10]

3. Each RIPE drug earns its place in the combination by acting differently: isoniazid and ethambutol both target cell-wall construction, but at different steps and with different potency against actively versus slowly dividing organisms; rifampin blocks the transcription machinery the organism needs regardless of its growth phase; and pyrazinamide's usefulness is tied to the acidic, macrophage-associated environment where slower-growing, semi-dormant bacilli persist. That range of mechanisms and growth-phase coverage - not any single drug's individual potency - is what allows the intensive phase to shorten overall treatment duration and reduce relapse. [7][10]

4. When tuberculosis is resistant to rifampin and isoniazid together (multidrug-resistant, or MDR-TB), treatment shifts to a longer list of second-line agents, including fluoroquinolones, the diarylquinoline bedaquiline, and repurposed drugs such as linezolid. Leprosy is managed by a completely separate WHO multidrug therapy built on dapsone, rifampin and clofazimine, chosen for activity against *Mycobacterium leprae* specifically rather than adapted from the tuberculosis regimen. [5][8]

Classification and drug examples

Intro: Antimycobacterials divide naturally into first-line tuberculosis drugs, second-line/MDR-TB agents, and antileprosy agents - three groups built around different resistance situations and, for leprosy, a different organism altogether.

1. Name: First-line antitubercular agents (RIPE)

1. Note: The four drugs combined in the intensive phase of standard drug-susceptible tuberculosis treatment.

1. Name: Isoniazid

INH

1. Route: Oral or intramuscular

1. Note: Prodrug activated by mycobacterial KatG; blocks mycolic acid synthesis. [1][7]

2. Name: Rifampin

1. Rifampicin

2. Rifadin

2. Route: Oral or intravenous

2. Note: Inhibits DNA-dependent RNA polymerase; potent CYP450 inducer. [2]

3. Name: Pyrazinamide

PZA

3. Route: Oral

3. Note: Mechanism unknown on its own label; active in the acidic intracellular environment. [3]

4. Name: Ethambutol

1. EMB

2. Myambutol

4. Route: Oral

4. Note: Bacteriostatic; defining toxicity is dose-related optic neuritis. [4] [10]

2. Name: Second-line / MDR-TB agents

2. Note: Reserved for tuberculosis resistant to first-line agents or when a first-line drug cannot be used; always combined with several other active drugs, never as monotherapy.

1. Name: Bedaquiline

Sirturo

1. Route: Oral

1. Note: Diarylquinoline; used for pulmonary TB resistant to at least rifampin and isoniazid, always with at least three other active drugs; QTc prolongation is the defining safety concern. [5]

2. Name: Linezolid

Zyvox

2. Route: Oral or intravenous

2. Note: An oxazolidinone repurposed from Gram-positive bacterial infection treatment into MDR-TB regimens. [10]

3. Name: Levofloxacin / Moxifloxacin

Fluoroquinolones

3. Route: Oral or intravenous

3. Note: Fluoroquinolones with antimycobacterial activity, used as core companion drugs in MDR-TB regimens. [10]

4. Name: Streptomycin

An injectable aminoglycoside

4. Route: Intramuscular

4. Note: One of the original antitubercular drugs; retains a role as an injectable second-line agent where used. [7] [5]

3. Name: Antileprosy agents (WHO multidrug therapy)

3. Note: Target Mycobacterium leprae specifically; combined for the same acquired-resistance-prevention logic used in tuberculosis, but with a different three-drug set.

1. Name: Dapsone

1. DDS

2. 4,4'-diaminodiphenylsulfone

1. Route: Oral

1. Note: Bacteriostatic/bactericidal against M. leprae; also used for dermatitis herpetiformis. Causes near-universal methemoglobinemia and can trigger hemolysis in G6PD deficiency. [6]

2. Name: Clofazimine

Lamprene

2. Route: Oral

2. Note: A fat-soluble, brick-red dye that binds mycobacterial DNA; causes the characteristic pinkish-brown skin and body-fluid discoloration seen with prolonged use. [9]

3. Name: Rifampin (leprosy regimen)

Rifampicin

3. Route: Oral

3. Note: The same drug used against M. tuberculosis is the third pillar of WHO leprosy multidrug therapy. [8] [8]

Mechanism of action

Summary: The first-line tuberculosis drugs attack different, largely non-overlapping targets in or around the mycobacterial cell: isoniazid and ethambutol interfere with cell-wall construction (mycolic acid synthesis and arabinogalactan assembly respectively), rifampin blocks the RNA polymerase needed for transcription, and pyrazinamide's converted active form works specifically in the acidic intracellular environment where semi-dormant bacilli persist. Antileprosy drugs use a different logic again: dapsone and rifampin act on folate metabolism and transcription respectively, while clofazimine binds mycobacterial DNA and adds an anti-inflammatory effect useful for leprosy's reactive skin complications.

Target: Mycolic acid and arabinogalactan cell-wall synthesis (isoniazid, ethambutol), DNA-dependent RNA polymerase (rifampin), an intracellular acid-dependent target of uncertain identity (pyrazinamide), and mycobacterial DNA (clofazimine)

Cidal Static: Isoniazid and rifampin are bactericidal against actively dividing M. tuberculosis; ethambutol is bacteriostatic; pyrazinamide's bactericidal or bacteriostatic behaviour depends on the drug concentration reached at the infection site

Kill Kinetics: Combination therapy over months is required because the mycobacterial cell wall slows drug penetration and because subpopulations of organisms grow at different rates and are killed by different drugs at different points in treatment

1. Step: 1

1. Title: Isoniazid is activated inside the organism

1. Detail: Isoniazid is a prodrug converted to its active form by the mycobacterial catalase-peroxidase enzyme KatG;

the activated drug then inhibits an enzyme in the mycolic acid synthesis pathway, weakening the cell wall of actively dividing bacilli. [7]

2. Step: 2

2. Title: Rifampin binds RNA polymerase

2. Detail: Rifampin inhibits DNA-dependent RNA polymerase activity in susceptible *M. tuberculosis*, blocking transcription regardless of how fast the organism is growing, which is why it contributes activity against both actively dividing and more dormant populations. [2]

3. Step: 3

3. Title: Pyrazinamide requires an acidic environment to work

3. Detail: Pyrazinamide is converted to its active form, pyrazinoic acid, and works best at the acidic pH found inside macrophage phagolysosomes, which is where the more slowly replicating bacilli often persist; its own FDA label states the precise mechanism beyond this is unknown. [3]

4. Step: 4

4. Title: Ethambutol impairs cell-wall metabolite synthesis

4. Detail: Ethambutol diffuses into actively growing mycobacterial cells and impairs the synthesis of cell-wall metabolites, arresting multiplication; this bacteriostatic action makes ethambutol useful mainly for suppressing the emergence of resistance to the other three drugs rather than for rapid bacterial killing on its own. [4]

5. Step: 5

5. Title: Antileprosy agents combine cell-target and immune effects

5. Detail: Against *M. leprae*, dapsone and rifampin contribute antimicrobial killing while clofazimine adds a distinct anti-inflammatory action - inhibiting T-lymphocyte activation and neutrophil motility - that is specifically useful for controlling the reactive skin inflammation (erythema nodosum leprosum) that can occur during leprosy treatment. [9]

Spectrum of activity

1. Subclass Id: first-line-tb

1. Coverage: *Mycobacterium tuberculosis*, the organism the entire RIPE regimen is built around; none of the four first-line drugs is used as a general-purpose antibacterial outside mycobacterial disease. [10]

2. Subclass Id: second-line-mdr

2. Coverage: Reserved for *M. tuberculosis* strains resistant to first-line agents (MDR-TB, defined as resistance to at least rifampin and isoniazid); bedaquiline's label restricts it to that resistant population specifically rather than drug-susceptible disease. [5]

3. Subclass Id: antileprosy

3. Coverage: *Mycobacterium leprae*, the separate organism causing leprosy; dapsone and clofazimine have essentially no established role in tuberculosis treatment despite the shared genus. [8]

Major clinical uses

1. Drug: Isoniazid

1. Organism: *Mycobacterium tuberculosis*

1. Indication: Active pulmonary and extrapulmonary tuberculosis (as part of a multidrug regimen); latent tuberculosis infection treatment alone or with rifapentine

1. Line: first-line

1. Note: Pyridoxine (vitamin B6) is commonly co-administered in patients predisposed to neuropathy. [1]

2. Drug: Rifampin

2. Organism: *Mycobacterium tuberculosis*

2. Indication: Active tuberculosis as part of a multidrug regimen; also used off-label as adjunctive therapy in some staphylococcal and *Neisseria meningitidis* carriage settings

2. Line: first-line

2. Note: Its CYP450-induction potential is a major factor in choosing companion drugs, especially antiretrovirals. [2]
3. Drug: Pyrazinamide
3. Organism: Mycobacterium tuberculosis
3. Indication: Intensive-phase (first 2 months) tuberculosis treatment as part of a multidrug regimen
3. Line: first-line, intensive phase only
3. Note: Not continued into the continuation phase of standard regimens. [10]
4. Drug: Ethambutol
4. Organism: Mycobacterium tuberculosis
4. Indication: Intensive-phase tuberculosis treatment, particularly while susceptibility results are pending
4. Line: first-line
4. Note: Its role is largely to prevent resistance to the other drugs while isoniazid susceptibility is confirmed. [10]
5. Drug: Bedaquiline
5. Organism: Mycobacterium tuberculosis resistant to rifampin and isoniazid
5. Indication: Pulmonary MDR-TB, as part of combination therapy with at least three other active drugs
5. Line: reserved, MDR-TB only
5. Note: Not indicated for drug-susceptible, latent, or extrapulmonary tuberculosis in its own label. [5]
6. Drug: Dapsone
6. Organism: Mycobacterium leprae
6. Indication: All forms of leprosy except proven dapsone-resistant cases, as part of WHO multidrug therapy; also used for dermatitis herpetiformis
6. Line: first-line for leprosy (with rifampin and clofazimine)
6. Note: G6PD status is relevant before starting given its hemolysis risk. [6]
7. Drug: Clofazimine
7. Organism: Mycobacterium leprae
7. Indication: Multibacillary leprosy as part of WHO multidrug therapy; also used for erythema nodosum leprosum reactions
7. Line: first-line for leprosy (with dapsone and rifampin)
7. Note: Its anti-inflammatory action is specifically useful for the reactive skin complication ENL. [9]

Pharmacokinetics

1. Drug: Isoniazid
1. Route: Oral or intramuscular
1. Absorption: Well absorbed orally
1. Csf Penetration: See prescribing reference
1. Metabolism: Hepatic acetylation (genetically variable fast/slow acetylators status)
1. Elimination: Renal, largely as metabolites
1. Dose Adjust: Hepatic impairment; risk of neuropathy in malnourished, alcoholic or diabetic patients drives pyridoxine co-administration rather than a dose change [1]
2. Drug: Rifampin
2. Route: Oral or intravenous
2. Absorption: Well absorbed orally
2. Csf Penetration: See prescribing reference
2. Metabolism: Hepatic; also a potent inducer of its own metabolism and that of numerous CYP450 substrates
2. Elimination: Biliary/fecal with some renal excretion
2. Dose Adjust: Hepatic impairment; extensive drug-interaction review is required before starting because of CYP induction [2]
3. Drug: Pyrazinamide

- 3. Route: Oral
- 3. Absorption: Well absorbed orally
- 3. Csf Penetration: See prescribing reference
- 3. Metabolism: Hepatic
- 3. Elimination: Renal
- 3. Dose Adjust: Hepatic impairment and pre-existing liver disease increase hepatotoxicity risk; baseline liver function and uric acid are checked before starting [3]
- 4. Drug: Ethambutol
- 4. Route: Oral
- 4. Absorption: Well absorbed orally
- 4. Csf Penetration: See prescribing reference
- 4. Metabolism: Partial hepatic
- 4. Elimination: Approximately 50% excreted unchanged in urine
- 4. Dose Adjust: Renal impairment requires dose reduction because the kidney is the principal excretion route and accumulation raises optic neuritis risk [4]
- 1. This page gives no dose regimens by design. Dosing, including weight-based mg/kg calculations and intermittent versus daily schedules, depends on the treatment phase, renal and hepatic function, and drug-susceptibility results, and belongs in a current prescribing reference used by the treating clinician.
- 2. Isoniazid's acetylator status (fast versus slow, a genetically determined trait) affects both drug exposure and toxicity risk, which is one reason isoniazid pharmacokinetics is a recurring exam topic distinct from the other three first-line drugs. [1]
- 3. Rifampin's CYP450 induction is the single pharmacokinetic property that most complicates co-prescribing across this entire drug class, particularly for antiretrovirals, oral contraceptives, warfarin and many other chronically used drugs. [2]

Adverse effects

- 1. Effect: Gastrointestinal upset
- 1. Detail: Nausea, anorexia and abdominal discomfort are reported across the first-line agents, particularly pyrazinamide and ethambutol. [3][4]
- 2. Effect: Orange-red body fluid discoloration
- 2. Detail: Rifampin discolors urine, sweat, tears, saliva and sputum; the color change is harmless but is an important counselling point, including a warning that it can permanently stain soft contact lenses. [2]
- 3. Effect: Asymptomatic hyperuricemia
- 3. Detail: Pyrazinamide inhibits renal excretion of urates, frequently causing hyperuricemia that is usually asymptomatic but can precipitate gout. [3]
- 1. Effect: Hepatotoxicity
- 1. Detail: Isoniazid, rifampin and pyrazinamide are all independently hepatotoxic, ranging from asymptomatic transaminase elevation to fulminant liver failure; pyrazinamide's hepatotoxicity is described as dose-related and can occur at any point during therapy.
- 1. Action: Baseline and periodic liver function testing, with treatment interruption for significant transaminase elevation or clinical hepatitis signs. [1][2][3]
- 2. Effect: Peripheral neuropathy (isoniazid)
- 2. Detail: A dose-related peripheral neuropathy occurs with isoniazid, more common in the malnourished, alcoholics and diabetics; it reflects a pyridoxine (vitamin B6)-antagonist effect of the drug.
- 2. Action: Pyridoxine is recommended concomitantly in patients predisposed to neuropathy. [1]
- 3. Effect: Optic neuritis (ethambutol)
- 3. Detail: Ethambutol can decrease visual acuity through optic neuritis, related to dose and duration; it is generally

reversible if the drug is stopped promptly, but irreversible blindness has been reported.

3. Action: Baseline visual acuity and color vision testing, repeated periodically and monthly at doses above 15 mg/kg/day; patients are told to report any visual change immediately. [4]

4. Effect: QTc prolongation (bedaquiline)

4. Detail: Bedaquiline can additively prolong the QTc interval, especially with other QT-prolonging drugs.

4. Action: ECG monitoring at baseline and during treatment; discontinue for significant ventricular arrhythmia or a QTc above 500 ms. [5]

5. Effect: Hemolysis and methemoglobinemia (dapsone)

5. Detail: Dapsone produces a rise in methemoglobin in almost all patients and can cause dose-related hemolysis and Heinz body formation, exaggerated in G6PD deficiency; deaths from agranulocytosis and other blood dyscrasias have been reported.

5. Action: G6PD status assessment before starting and monitoring for hemolytic or blood-count abnormalities during treatment. [6]

6. Effect: Skin and body-fluid discoloration (clofazimine)

6. Detail: Clofazimine, itself a brick-red dye, produces a pinkish-brown discoloration of skin and body fluids in most patients treated beyond a month; the change typically fades after stopping the drug but can persist for months to years.

6. Action: This is disclosed to patients before starting as an expected, generally reversible cosmetic effect rather than a sign of toxicity. [9]

1. Drug: Isoniazid

1. Effect: The class member most associated with hepatitis and dose-related peripheral neuropathy, the latter specifically preventable with pyridoxine. [1]

2. Drug: Rifampin

2. Effect: The only first-line drug whose defining pharmacological property is CYP450 induction rather than a direct organ toxicity, alongside the characteristic body-fluid discoloration. [2]

3. Drug: Ethambutol

3. Effect: The only first-line drug with optic neuritis as its signature, dose-related toxicity requiring dedicated visual monitoring. [4]

4. Drug: Bedaquiline

4. Effect: The class member specifically restricted to MDR-TB and always used with at least three other active drugs because of its QTc-prolongation risk. [5]

Contraindications, precautions and interactions

1. Dapsone: proven dapsone-resistant leprosy is a reason the drug will not achieve its intended purpose, functionally excluding it from that specific regimen. [6]

2. Pyrazinamide: acute gout is a contraindication, given the drug's tendency to raise serum uric acid. [3]

1. Pre-existing liver disease is a caution across isoniazid, rifampin and pyrazinamide, given the independent hepatotoxicity risk each carries. [1][2][3]

2. Renal impairment requires ethambutol dose reduction because of its largely renal elimination and the accumulation-related optic neuritis risk. [4]

3. G6PD deficiency is specifically relevant to dapsone given its hemolysis risk. [6]

4. A history of QTc prolongation or concomitant QT-prolonging drugs is weighed carefully before starting bedaquiline. [5]

1. With: Antiretrovirals, oral contraceptives, warfarin, azole antifungals and many other CYP450 substrates

1. Effect: Rifampin's induction of CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4 can substantially lower the levels of these co-administered drugs, requiring dose adjustment, an alternative agent, or careful monitoring. [2]

2. With: Other QT-prolonging drugs

2. Effect: Additive QTc prolongation with bedaquiline; concomitant use is reviewed carefully and ECG monitoring

intensified. [5]

3. With: Alcohol

3. Effect: Increases hepatotoxicity risk with isoniazid, rifampin and pyrazinamide and increases isoniazid neuropathy risk. [1]

Resistance mechanisms

1. Mechanism: KatG mutation (isoniazid)

1. Detail: Because isoniazid is a prodrug requiring activation by the mycobacterial catalase-peroxidase KatG, mutations that reduce or abolish KatG activity prevent the drug from ever being converted to its active form, producing resistance. [7]

2. Mechanism: RNA polymerase (rpoB) mutation (rifampin)

2. Detail: Mutations in the rpoB gene encoding the RNA polymerase beta subunit reduce rifampin binding, which is why rifampin resistance is used clinically as a proxy marker for MDR-TB risk in rapid molecular testing. [10]

3. Mechanism: Sequential single-drug exposure

3. Detail: Because a large natural bacterial population always contains some organisms resistant to any one drug, treating with a single agent selects for and amplifies that resistant subpopulation; multidrug combination therapy is the deliberate strategy used to prevent this, which is the core rationale for the RIPE regimen and for WHO leprosy multidrug therapy alike. [10][8]

4. Mechanism: Multidrug-resistant and beyond

4. Detail: Resistance to at least rifampin and isoniazid together defines MDR-TB, which shifts treatment onto second-line agents such as bedaquiline, fluoroquinolones and linezolid, always in combination. [5]

Comparison tables

Title: RIPE at a glance

Caption: The four first-line drugs cover different growth-phase populations and carry distinct signature toxicities, which is why all four are combined rather than any one substituted for another.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: target

2. Label: Primary target

3. Key: signature_toxicity

3. Label: Signature toxicity

4. Key: monitoring

4. Label: Key monitoring

1. Drug: Isoniazid

1. Target: Mycolic acid synthesis (activated prodrug)

1. Signature Toxicity: Hepatitis; dose-related peripheral neuropathy

1. Monitoring: Liver function; pyridoxine in at-risk patients [1]

2. Drug: Rifampin

2. Target: DNA-dependent RNA polymerase

2. Signature Toxicity: Hepatotoxicity; orange-red body fluids

2. Monitoring: Liver function; drug-interaction review [2]

3. Drug: Pyrazinamide

3. Target: Unknown; requires acidic intracellular pH

3. Signature Toxicity: Dose-related hepatotoxicity; hyperuricemia

3. Monitoring: Liver function; serum uric acid [3]

- 4. Drug: Ethambutol
- 4. Target: Cell-wall metabolite synthesis
- 4. Signature Toxicity: Dose-related optic neuritis
- 4. Monitoring: Visual acuity and color vision, baseline and periodic [4]

High-yield exam pearls

- 1. Pearl: RIPE is combined for two months, then continued as rifampin plus isoniazid alone for the rest of standard treatment.
- 1. Why: This intensive-phase/continuation-phase structure is the most commonly tested regimen shape for drug-susceptible tuberculosis. [10]
- 2. Pearl: Only ethambutol has a defining ophthalmologic toxicity among the RIPE drugs.
- 2. Why: Optic neuritis with visual acuity and color-vision loss is specific enough to ethambutol that it is a reliable single-best-answer clue on exams. [4]
- 3. Pearl: Pyridoxine (vitamin B6) is given with isoniazid to prevent peripheral neuropathy, not to treat the tuberculosis itself.
- 3. Why: It is a frequently tested pairing that distinguishes a supportive co-medication from an antitubercular drug. [1]
- 4. Pearl: Rifampin's mechanism (RNA polymerase inhibition) is unrelated to its most clinically disruptive property (CYP450 induction) - the two are separate pharmacological facts about the same drug.
- 4. Why: Exam questions often test whether the mechanism of antitubercular action is being confused with the mechanism of the drug interaction. [2]
- 5. Pearl: Pyrazinamide's own FDA label states its mechanism of action is unknown.
- 5. Why: This is worth remembering precisely because many other sources imply a settled mechanism; the primary label does not claim one. [3]
- 6. Pearl: Leprosy multidrug therapy (dapsone, rifampin, clofazimine) is a distinct regimen from tuberculosis's RIPE, despite both diseases being mycobacterial.
- 6. Why: It is a common trap to assume one mycobacterial regimen applies to both diseases. [8]

Common exam traps

- 1. Trap: Assuming rifampin's antitubercular mechanism explains its drug interactions.
- 1. Correction: Rifampin kills M. tuberculosis by inhibiting RNA polymerase; it disrupts other drugs' levels through a completely separate property, CYP450 enzyme induction. [2]
- 2. Trap: Attributing peripheral neuropathy to ethambutol instead of isoniazid.
- 2. Correction: Ethambutol's defining neurologic toxicity is optic neuritis affecting vision; dose-related peripheral neuropathy is isoniazid's signature toxicity, managed with pyridoxine. [4][1]
- 3. Trap: Treating pyrazinamide as if it is continued for the full duration of tuberculosis treatment.
- 3. Correction: Pyrazinamide is used only in the intensive first-line phase (commonly the first two months), not the continuation phase. [10]
- 4. Trap: Assuming leprosy is treated with the same RIPE regimen as tuberculosis because both are caused by mycobacteria.
- 4. Correction: Leprosy uses WHO multidrug therapy built on dapsone, rifampin and clofazimine - a different three-drug combination chosen for Mycobacterium leprae, not the four-drug RIPE regimen for M. tuberculosis. [8]
- 5. Trap: Believing bedaquiline can be used as monotherapy for MDR-TB.
- 5. Correction: Bedaquiline's own label restricts it to use as part of combination therapy with at least three other drugs to which the patient's isolate is susceptible, given the risk of amplifying resistance and its QTc-prolongation profile. [5]

Self-test questions

1. Question: Which first-line tuberculosis drug is a prodrug that must be activated by the mycobacterial enzyme KatG?

1. Rifampin
2. Isoniazid
3. Ethambutol
4. Pyrazinamide

1. Explanation: Isoniazid requires activation by the mycobacterial catalase-peroxidase KatG before it can inhibit mycolic acid synthesis; mutations in KatG are a major cause of isoniazid resistance. [7]

2. Question: Which first-line drug's own FDA label states that its mechanism of action is unknown?

1. Ethambutol
2. Rifampin
3. Pyrazinamide
4. Isoniazid

2. Explanation: Pyrazinamide's label states the mechanism is unknown, while noting the drug requires an acidic environment and depends on conversion to pyrazinoic acid for activity. [3]

3. Question: A patient on rifampin reports orange-tinted urine and tears. What is the appropriate response?

1. Stop rifampin immediately for suspected hepatotoxicity
2. Reassure the patient this is an expected, harmless effect of the drug
3. Order an urgent renal function panel
4. Switch to isoniazid alone

3. Explanation: Rifampin's label describes discoloration of urine, sweat, sputum and tears as an expected effect, not a sign of toxicity, though patients should be counselled about it in advance, including the risk of permanently staining soft contact lenses. [2]

4. Question: Which toxicity is most specifically associated with ethambutol among the first-line tuberculosis drugs?

1. Peripheral neuropathy
2. Hyperuricemia
3. Optic neuritis
4. QTc prolongation

4. Explanation: Ethambutol's defining, dose-related toxicity is optic neuritis with decreased visual acuity and color-vision changes, monitored with baseline and periodic visual testing. [4]

5. Question: What is the standard WHO multidrug therapy combination for leprosy?

1. Rifampin, isoniazid, pyrazinamide
2. Dapsone, rifampin, clofazimine
3. Bedaquiline, linezolid, moxifloxacin
4. Ethambutol, dapsone, isoniazid

5. Explanation: Leprosy (Hansen disease) is treated with a WHO multidrug regimen of dapsone, rifampin and clofazimine, a combination distinct from the RIPE regimen used for tuberculosis. [8]

6. Question: Why is bedaquiline never given as a single added drug to a failing regimen?

1. It has no antimycobacterial activity of its own
2. Its label requires it be used with at least three other active drugs, partly to avoid amplifying resistance while managing its QTc-prolongation risk
3. It is only approved for latent tuberculosis
4. It cannot be taken orally

6. Explanation: Bedaquiline's prescribing information restricts its use to combination therapy with at least three other drugs the isolate is susceptible to, both to prevent resistance amplification and because of its own cardiac safety profile requiring ECG monitoring. [5]

Frequently asked questions

1. Question: Why are four drugs used together for tuberculosis instead of one strong drug?

1. Answer: Any single antitubercular drug used alone will eventually fail because a small number of naturally resistant organisms in a large bacterial population survive and repopulate the infection. Combining drugs with different mechanisms and different activity against fast- versus slow-growing bacilli prevents that resistant subpopulation from taking over, which is the entire rationale for the RIPE regimen and for WHO's multidrug approach to leprosy as well. [10][8]

2. Question: Why does isoniazid sometimes come with a vitamin B6 tablet?

2. Answer: Isoniazid can cause a dose-related peripheral neuropathy, more common in malnourished patients, alcoholics and diabetics. Pyridoxine (vitamin B6) is given alongside isoniazid in patients predisposed to this effect; it treats a side effect of isoniazid rather than contributing to the antitubercular effect itself. [1]

3. Question: Is the orange-red discoloration from rifampin dangerous?

3. Answer: No - rifampin's own prescribing information describes discoloration of urine, sweat, saliva, sputum and tears as an expected, harmless effect, though patients should be told about it in advance, including that it can permanently stain soft contact lenses. [2]

4. Question: Why does ethambutol require eye exams during treatment?

4. Answer: Ethambutol can cause dose-related optic neuritis, with decreased visual acuity and color-vision changes; this is generally reversible if caught early and the drug is stopped, but irreversible blindness has been reported when it is not. Baseline and periodic visual acuity and color-vision testing - monthly if the dose exceeds 15 mg/kg/day - is how this risk is managed. [4]

5. Question: Is leprosy treated with the same drugs as tuberculosis?

5. Answer: No. Although both diseases are caused by mycobacteria, leprosy (Hansen disease) uses a separate WHO multidrug therapy built on dapsone, rifampin and clofazimine, targeted at *Mycobacterium leprae*. Tuberculosis uses the four-drug RIPE combination targeted at *Mycobacterium tuberculosis*. Rifampin is the one drug common to both regimens. [8]

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