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A Study on Rifampin as a Potent Anti-Tubercular Drug

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Abstract

Rifampicin (rifampin) is a semi-synthetic rifamycin antibiotic and one of the most important first-line drugs for the treatment of tuberculosis and leprosy. Structurally, it is an ansamycin in which a naphthohydroquinone chromophore is spanned by a long aliphatic ansa bridge, and its 3-(4-methylpiperazinyl) iminomethyl side chain confers oral activity. Rifampicin binds to the β -subunit of bacterial DNA-dependent RNA polymerase and sterically blocks the elongating RNA transcript, producing bactericidal and sterilising activity against both actively replicating and semi-dormant *Mycobacterium tuberculosis*. Owing to its high oral bioavailability and excellent tissue penetration, it is also used for meningococcal and *Haemophilus influenzae* type b chemoprophylaxis, implant-associated staphylococcal infections, brucellosis, non-tuberculous mycobacterial infections and *Rhodococcus equi* infection in foals. Its clinical use is limited by hepatotoxicity, potent induction of cytochrome P450 enzymes and drug transporters, and the rapid selection of resistance when used as monotherapy. Resistance arises mainly from mutations in the 81-bp rifampicin resistance-determining region of the *rpoB* gene, and rifampicin resistance is now the defining marker of multidrug-resistant tuberculosis. This review summarises the history, chemistry, mechanism of action, pharmacokinetics, formulations, clinical applications, safety, resistance and environmental impact of rifampicin, and outlines the scope for future research, including high-dose regimens, shortened rifamycin-based therapy, nanocarrier delivery systems and remediation of rifampicin residues in the environment.

Key words : Rifampicin; Rifamycins; Tuberculosis; RNA polymerase inhibition; *rpoB* mutation; Antimicrobial resistance; Drug delivery.

1. Introduction

Tuberculosis (TB) remains one of the leading infectious causes of death worldwide. According to the World Health Organization (WHO), an estimated 390 000 people developed multidrug- or rifampicin-resistant TB (MDR/RR-TB) in 2024, and MDR/RR-TB was present in 3.2% of new and 16% of previously treated TB cases¹. Rifampicin, also known as rifampin, is the backbone of the standard 6-month regimen for drug-susceptible TB, and its introduction made short-course chemotherapy possible^{2,3}. It belongs to the rifamycin class of antibiotics and is strongly bactericidal, killing bacteria rather than merely inhibiting their growth.

Besides TB, rifampicin is a component of multidrug therapy for leprosy, a chemoprophylactic agent against *Neisseria meningitidis* and *Haemophilus influenzae* type b, and an adjunct in the treatment of biofilm-associated staphylococcal infections. These benefits are offset by hepatotoxicity, extensive drug–drug interactions and the rapid emergence of resistance when the drug is used alone. The present review gives a concise, consolidated account of the history, chemistry, mechanism of action, pharmacokinetics, formulations, clinical applications, adverse effects, resistance and environmental considerations of rifampicin, followed by the scope for future research.

2. Historical Background

The rifamycins were discovered in 1957 at the Lepetit research laboratories in Milan, Italy, from a soil actinomycete originally named *Streptomyces mediterranei*, which was later reclassified in the genus *Amycolatopsis* (*A. rifamycinica*)^{3,4}. The name “rifamycin” was inspired by the French film *Rififi*. The first fermentation products, chiefly rifamycin B, had limited activity and could not be given orally, so a systematic programme of chemical modification was undertaken^{3,5}.

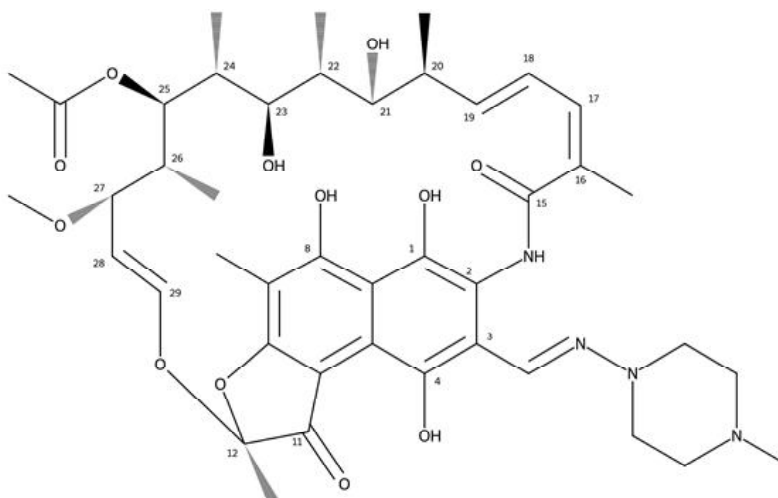
Rifamycin SV became the first rifamycin used clinically, but it was poorly absorbed after oral administration. Condensation of 3-formylrifamycin SV with 1-amino-4-methylpiperazine gave rifampicin, which was synthesised in 1965 and reported in 1966 as a new orally active rifamycin⁶. Rifampicin entered clinical practice in Italy in 1968 and in the United States in 1971³. When combined with isoniazid, it shortened TB treatment from 18–24 months to 6–9 months. The structural complexity of the rifamycins later made them classic targets for total synthesis, culminating in Kishi's total synthesis of rifamycin S⁷. Rifampicin remains on the WHO Model List of Essential Medicines⁸.

3. Chemistry and Structure of Rifampicin

3.1. Structural features :

Rifampicin (**1**, Fig. 1) is chemically 3-[[[4-methyl-1-piperazinyl]imino]methyl]rifamycin^{9,10}. It is an ansamycin: an aromatic naphthohydroquinone (naphthofuranone) chromophore bridged by a 17-atom aliphatic ansa chain (C15–C29). The chain is attached to the chromophore through an amide nitrogen at C2 and through an enol ether oxygen at the C12 ketal carbon^{5,11,12}. The molecule contains

nine stereogenic centres (C12, C20–C27) and four stereodefined double bonds (16Z, 18E, 28E and the E-configured hydrazone at C3). The free hydroxyl groups at C1, C8, C21 and C23 form hydrogen bonds with the RNA polymerase β -subunit, and the C25 acetoxy and C27 methoxy groups complete the ansa bridge¹³. The 3-(4-methylpiperazinyl)iminomethyl substituent, absent in the parent rifamycin SV (**2**), is responsible for the improved oral absorption and longer half-life of rifampicin^{6,14}.



Rifampicin (1)

$C_{43}H_{58}N_4O_{12}$ | $M_r = 822.94 \text{ g mol}^{-1}$ | CAS 13292-46-1

Fig. 1. Chemical structure of rifampicin (**1**) showing the rifamycin numbering of the naphthofuranone chromophore and of the ansa bridge (C15–C29), the absolute configuration of the nine stereocentres (wedged and hashed bonds), the geometry of the double bonds and the 3-(4-methylpiperazinyl)iminomethyl side chain. Structure drawn by the author from the reference InChIKey JQXXHWHPUNPDRT-WLSIYKJHSA-N⁹.

3.2. Physicochemical properties :

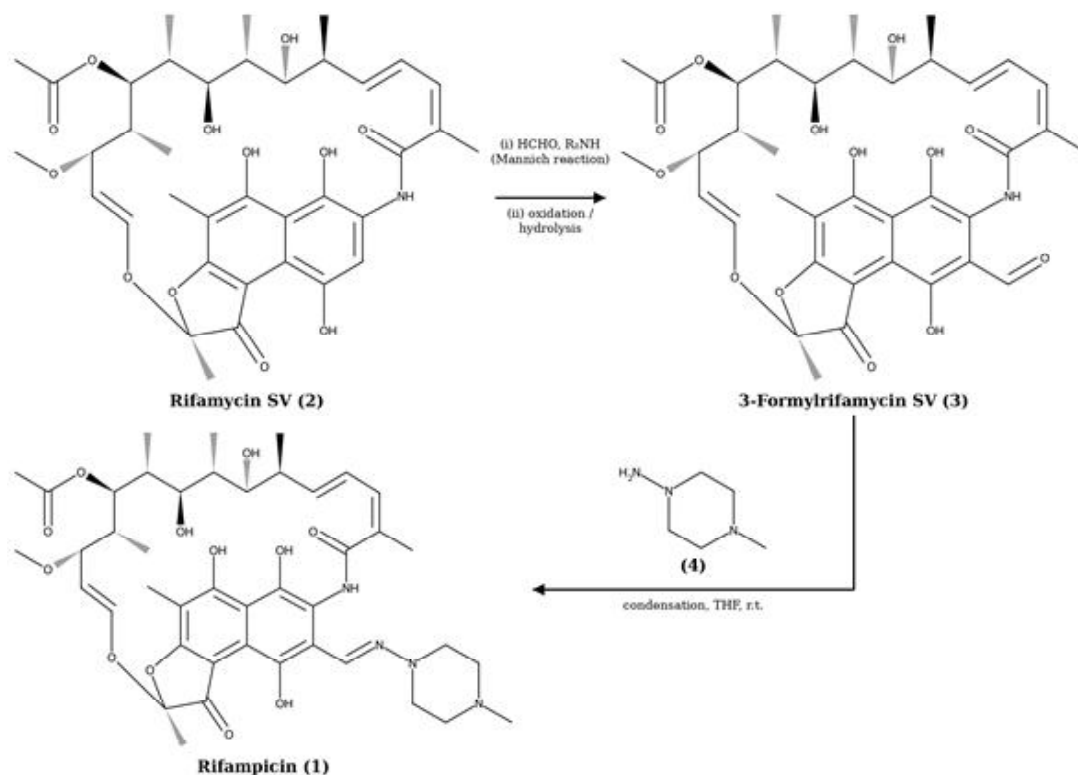
Rifampicin is a red to reddish-brown crystalline powder. It is amphoteric, with a weakly acidic 4-hydroxyl group ($pK_a \approx 1.7$) and a basic piperazine nitrogen ($pK_a \approx 7.9$), and therefore exists largely as a zwitterion at physiological pH [10, 15]. Its low aqueous solubility and high permeability place it in Biopharmaceutics Classification System (BCS) class II. Its main identifiers and properties are summarised in Table 1.

3.3. Semi-synthesis :

Rifampicin is produced semi-synthetically from fermentation-derived rifamycins (Fig. 2). Rifamycin B, produced by *Amycolatopsis* strains, is converted through rifamycin O and S into rifamycin SV (**2**). A Mannich reaction of **2** with formaldehyde and a secondary amine, followed by oxidation and hydrolysis of the resulting Mannich base, gives 3-formylrifamycin SV (**3**). Condensation of the C3 aldehyde of **3** with 1-amino-4-methylpiperazine (**4**) forms the hydrazone linkage of rifampicin (**1**)^{5,6}.

Table 1. Chemical identity and physicochemical properties of rifampicin (**1**)^{9,10,16}.

Property	Value
International non-proprietary name (INN) / USAN	Rifampicin / Rifampin
Chemical name	3-[[[(4-Methyl-1-piperazinyl)imino]methyl]rifamycin
Molecular formula	C ₄₃ H ₅₈ N ₄ O ₁₂
Relative molecular mass	822.94 g mol ⁻¹
CAS Registry Number	13292-46-1
PubChem CID / DrugBank ID	135398735 / DB01045
Standard InChIKey	JQXXHWHPUNPDRT-WLSIYKJHSA-N
ATC code	J04AB02
Appearance	Red to reddish-brown crystalline powder
Melting point	183–188 °C (with decomposition)
Solubility	Very slightly soluble in water; soluble in chloroform, methanol and dimethyl sulfoxide
pK _a values	≈ 1.7 (4-OH); ≈ 7.9 (piperazine N)
BCS class	Class II (low solubility, high permeability)

**Fig. 2.** Semi-synthetic route to rifampicin. Rifamycin SV (**2**) is converted into 3-formylrifamycin SV (**3**) by (i) a Mannich reaction (HCHO, R₂NH) and (ii) oxidation/hydrolysis; condensation of **3** with 1-amino-4-methylpiperazine (**4**) gives rifampicin (**1**). Scheme drawn by the author based on refs.^{5,6}.

4. Mechanism of Action :

Rifampicin inhibits bacterial transcription. It binds with high affinity to the β -subunit (encoded by *rpoB*) of the bacterial DNA-dependent RNA polymerase (RNAP) holoenzyme. The binding pocket lies within the DNA/RNA channel, about 12 Å from the catalytic Mg^{2+} centre^{13,17}. Crystal structures of the RNAP–rifampicin complex show that rifampicin does not prevent promoter binding or formation of the first phosphodiester bond. Instead, it sterically blocks the path of the growing RNA chain once the transcript reaches a length of two to three nucleotides, so that elongation is aborted. This “steric-occlusion” mechanism explains why rifampicin is active only against initiating, and not against already elongating, RNAP complexes¹³.

Inhibition of mRNA synthesis stops protein synthesis and leads to bacterial cell death, so rifampicin is bactericidal. Mammalian nuclear RNA polymerases are not inhibited at therapeutic concentrations, which accounts for the selective toxicity of the drug¹⁸. Rifampicin penetrates macrophages and caseous lesions and kills semi-dormant bacilli that show only intermittent metabolic activity. This sterilising activity is what allows TB treatment to be shortened to six months^{2,5}.

5. Pharmacokinetics, Dosage and Duration of Therapy :

Rifampicin is well absorbed after oral administration and reaches peak plasma concentrations in 2–4 h. Food delays and reduces absorption, so the drug is preferably taken 1 h before or 2 h after a meal^{15,19}. It is about 80% protein-bound and distributes widely into lung, bone, pleural fluid, macrophages and, when the meninges are inflamed, cerebrospinal fluid. In the liver it is deacetylated to the active metabolite 25-O-desacetyl-rifampicin and is excreted mainly in bile, with enterohepatic recirculation. Its elimination half-life of about 3–5 h falls during the first weeks of treatment because rifampicin induces its own metabolism (auto-induction)¹⁵. Rifampicin and its metabolites colour urine, sweat, tears and saliva orange-red, and patients should be warned of this in advance¹⁹.

For drug-susceptible pulmonary TB, rifampicin (10 mg/kg/day, maximum 600 mg) is given with isoniazid, pyrazinamide and ethambutol for an intensive phase of 2 months, followed by rifampicin plus isoniazid for a 4-month continuation phase^{2,20}. Longer treatment (9–12 months) is recommended for TB meningitis and osteoarticular TB. Regimens for rifampicin-resistant TB do not contain rifampicin. The recommended doses and durations for the main indications are summarised in Table 2. Doses must not be missed, the full course must be completed, and alcohol should be avoided during therapy, because incomplete treatment is the main driver of acquired resistance².

6. Pharmaceutical Formulations and Storage :

Rifampicin is available as capsules and tablets (commonly 150, 300, 450 and 600 mg), as an oral suspension (100 mg/5 mL) for children, and as a sterile lyophilised powder (600 mg) for intravenous infusion in patients who cannot take oral medication^{16,19}. Fixed-dose combinations (FDCs) of rifampicin with isoniazid, with or without pyrazinamide and ethambutol, are recommended by WHO because

Table 2. Usual dosage and duration of rifampicin therapy for its main indications in adults^{2,19–22}.

Indication	Usual adult dose (combination partners)	Duration
Drug-susceptible pulmonary TB	10 mg/kg/day (max. 600 mg) with isoniazid, pyrazinamide, ethambutol (intensive phase); with isoniazid (continuation phase)	6 months (2 + 4)
TB meningitis / osteoarticular TB	As above; higher doses under evaluation	9–12 months
Latent TB infection (4R regimen)	10 mg/kg/day (max. 600 mg), alone	4 months
Leprosy (WHO MDT)	600 mg once monthly (supervised) with dapsone and clofazimine	6 months (PB); 12 months (MB)
Meningococcal chemoprophylaxis	600 mg every 12 h	2 days
<i>H. influenzae</i> type b chemoprophylaxis	20 mg/kg once daily (max. 600 mg)	4 days
Prosthetic joint staphylococcal infection	300–450 mg twice daily with a partner antibiotic	Several weeks to months

they simplify treatment, improve adherence and prevent inadvertent monotherapy². Rifampicin is marketed worldwide under several brand names, including Rifadin® and Rimactane® for single-drug products, and Rifinah® (rifampicin + isoniazid) and Rifater® (rifampicin + isoniazid + pyrazinamide) for combinations. In India, it is also widely available as generic and FDC preparations (e.g., R-Cin®). Rifampicin is sensitive to light, moisture and acidic conditions. In the acidic environment of the stomach, particularly in the presence of isoniazid, it can hydrolyse to 3-formylrifamycin SV (3). Rifampicin products should therefore be stored in tightly closed, light-resistant (amber) containers at controlled room temperature, below 25 °C¹⁶. Reconstituted intravenous solutions should be used within the time stated by the manufacturer. Expired or degraded products should not be used, because loss of potency can contribute to treatment failure.

7. Clinical and Other Applications :

7.1. Tuberculosis, including immunocompromised patients :

Tuberculosis is the principal indication for rifampicin, which is effective against intracellular and extracellular bacilli in both pulmonary and extrapulmonary disease^{2,20}. People living with HIV and other immunocompromised patients (e.g., transplant recipients and patients receiving immunosuppressive therapy) are at high risk of active TB and benefit greatly from rifamycin-containing regimens. However, rifampicin lowers the plasma concentrations of many antiretroviral agents, so regimens must be selected carefully or rifabutin used instead²³. For latent TB infection, four months of daily rifampicin (4R) was as effective as nine months of isoniazid, with better completion rates and less hepatotoxicity²¹.

7.2. *Leprosy* :

Rifampicin is the most rapidly bactericidal drug against *Mycobacterium leprae*. In WHO multidrug therapy (MDT), a supervised monthly 600 mg dose is combined with dapson and clofazimine for 6 months in paucibacillary leprosy and for 12 months in multibacillary leprosy²².

7.3. *Chemoprophylaxis* :

Rifampicin eradicates nasopharyngeal carriage of *N. meningitidis* and *H. influenzae* type b. It is therefore used as chemoprophylaxis for close contacts of patients with invasive meningococcal or Hib disease, interrupting further transmission in households and institutions^{10,19}.

7.4. *Staphylococcal and device-associated infections* :

Rifampicin is highly active against *Staphylococcus aureus*, including methicillin-resistant strains (MRSA), and is one of the few antibiotics that kill bacteria within biofilms. In a randomised controlled trial, adding rifampicin to ciprofloxacin cured orthopaedic implant-related staphylococcal infections without removal of the implant²⁴. It is also used in combination therapy for prosthetic valve endocarditis and osteomyelitis. It must never be used alone, because resistance develops quickly.

7.5. *Brucellosis and other infections* :

Doxycycline plus rifampicin is an established regimen for human brucellosis²⁵. Rifampicin is also part of combination therapy for *Mycobacterium avium* complex and *M. kansasii* infections, which are particularly common in immunocompromised patients¹⁹.

7.6. *Veterinary and research applications* :

In veterinary medicine, rifampicin combined with a macrolide (erythromycin, azithromycin or clarithromycin) is the standard treatment for *Rhodococcus equi* pneumonia in foals²⁶. It is also used for selected staphylococcal and deep-seated infections in dogs and cats. Rifampicin is not used as a growth promoter, and its agricultural use is minimal. In the laboratory, it is widely used as a selective agent in microbiology and as a tool to study transcription and resistance mechanisms⁵.

8. *Adverse Effects, Drug Interactions and Contraindications* :

Rifampicin is generally well tolerated. Common adverse effects include harmless orange-red discolouration of body fluids (which can permanently stain soft contact lenses), gastrointestinal upset (nausea, vomiting, abdominal pain, diarrhoea, anorexia), rash and pruritus¹⁹. The most important adverse effect is hepatotoxicity, ranging from asymptomatic rises in transaminases and bilirubin to clinical hepatitis. The risk is greater when rifampicin is combined with isoniazid and pyrazinamide, and in elderly patients, those who consume alcohol regularly and those with pre-existing liver disease. Baseline and periodic liver function tests are therefore recommended for patients at risk²⁰. Intermittent or

interrupted therapy can provoke immune-mediated reactions, including a flu-like syndrome, thrombocytopenia, haemolytic anaemia and acute kidney injury¹⁹.

Rifampicin is one of the most potent known inducers of hepatic and intestinal cytochrome P450 enzymes (especially CYP3A4) and of P-glycoprotein. Through this induction it reduces the plasma concentrations and efficacy of many co-administered drugs, including hormonal contraceptives, warfarin, azole antifungals, HIV protease inhibitors, calcineurin inhibitors (ciclosporin, tacrolimus), corticosteroids, methadone and several anticonvulsants²³. Doses of such drugs may need adjustment, or alternative agents may be needed. Rifampicin is contraindicated in patients with hypersensitivity to rifamycins and in those with jaundice or severe hepatic impairment. It should not be re-introduced after serious immune-mediated reactions such as thrombocytopenia or haemolysis, and it should not be co-administered with certain protease inhibitors (e.g., saquinavir/ritonavir)^{10, 23}. During pregnancy, the benefit of treating TB outweighs the risk, but vitamin K may be needed for the mother and newborn when rifampicin is given in late pregnancy¹⁹.

9. Resistance to Rifampicin :

In *M. tuberculosis*, more than 95% of rifampicin-resistant isolates carry mutations in an 81-bp rifampicin resistance-determining region (RRDR) of *rpoB* (codons 507–533 in *E. coli* numbering)²⁷. The most frequent substitutions occur at codons 531 (S531L), 526 (H526Y/D) and 516 (D516V). These mutations alter the rifampicin-binding pocket of RNAP and reduce drug affinity without abolishing enzyme function^{5,13}. Because spontaneous resistance mutations occur at a frequency of about 10⁻⁸ per bacterium, monotherapy rapidly selects resistant mutants, which is why rifampicin is always used in combination¹⁸. In other bacteria, inactivation of the drug by ADP-ribosylation, glycosylation or phosphorylation, and efflux, also contribute to resistance⁵.

Rifampicin resistance in TB is usually accompanied by isoniazid resistance, and it is therefore used as the marker of MDR-TB. Molecular assays that detect RRDR mutations, such as Xpert MTB/RIF, allow rapid diagnosis of rifampicin resistance. The main causes of acquired resistance are missed doses, premature discontinuation, inadequate dosing, poor-quality drugs and inadvertent monotherapy. Directly observed treatment, fixed-dose combinations, universal drug-susceptibility testing and antimicrobial stewardship are therefore essential to preserve the efficacy of rifampicin^{1,2}.

10. Environmental Considerations :

Rifampicin residues reach soil and surface waters through hospital and household effluents, excretion by treated humans and animals, improper disposal of unused medicines and discharges from pharmaceutical manufacturing. Even sub-inhibitory concentrations can disturb natural microbial communities and select for resistant bacteria and resistance genes, which can then move between environmental, animal and human reservoirs. Expired or unused medicines should therefore be returned through take-back schemes rather than flushed or discarded with household waste, and manufacturing effluents require effective treatment. Advanced oxidation and photocatalytic processes are being

developed to degrade rifampicin in wastewater; for example, Mg-doped CuO nanocomposites recently achieved efficient photodegradation of rifampicin in real effluents²⁸.

11. Conclusion

More than five decades after its introduction, rifampicin remains one of the most important antibacterial drugs in clinical use. Its ansamycin structure, with a naphthohydroquinone chromophore spanned by an ansa bridge and a 3-(4-methylpiperazinyl)iminomethyl side chain, gives it high-affinity binding to bacterial RNA polymerase, good oral bioavailability and excellent tissue penetration. These properties make it indispensable for short-course TB therapy, leprosy MDT, chemoprophylaxis and biofilm-associated staphylococcal infections. Its hepatotoxicity, extensive drug–drug interactions and the ease with which *rpoB* mutations confer resistance call for combination therapy, careful monitoring and good adherence. Responsible stewardship and proper disposal of residues are equally necessary to preserve the long-term effectiveness of rifampicin.

12. Scope for Future Research :

Several areas of research are expected to shape the future use of rifampicin:

- **Dose optimisation:** Higher rifampicin doses have shown faster sputum culture conversion with acceptable safety in meta-analyses, but the optimal dose for TB meningitis, children and people with HIV still needs to be defined in phase III trials²⁹.
- **Treatment shortening:** A 4-month regimen containing the long-acting rifamycin rifapentine plus moxifloxacin was non-inferior to the standard 6-month regimen³⁰. Further rifamycin-based regimens for shortening drug-susceptible TB and latent TB treatment need to be developed²¹.
- **Advanced delivery systems:** Nanoemulsions, liposomes, polymeric and lipid nanoparticles and inhalable formulations could improve the solubility and macrophage targeting of rifampicin and reduce its systemic toxicity. Co-encapsulation with agents such as quercetin is one example of this approach³¹.
- **New rifamycin analogues:** Structure-based design of rifamycins that retain activity against common *rpoB* mutants (e.g., S531L) and that cause less CYP3A4 induction is needed^{5,13}.
- **Precision medicine:** Therapeutic drug monitoring, pharmacogenomics of drug transporters and rapid sequencing-based resistance testing could help individualise rifampicin dosing and detect resistance early¹.
- **Environmental remediation:** Low-cost photocatalytic and adsorptive materials for removing rifampicin residues from pharmaceutical and hospital wastewater, together with monitoring of environmental resistance genes, are needed²⁸.

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Conflict of interest: The author declares no conflict of interest.

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Data availability: No new data were generated in this review. Figures 1 and 2 were drawn by the author.

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