



Journal of Advanced Pharmaceutical Sciences and Natural Products (JAPSNP)

MANAGING RIFAMPICIN-BASED DRUG INTERACTIONS IN TUBERCULOSIS CO-TREATMENT: MECHANISTIC BASIS, CLASS-BY-CLASS MANAGEMENT STRATEGIES AND DECISION SUPPORT FOR HIGH-BURDEN SETTINGS

Dr. Shivaraj D R^{1*}

Ms. Harshitha N L²

Ms. Rachana M A²

Ms. T Pushpanjali²

^{1}Assistant Professor, Department of Pharmacy Practice, Akshaya Institute of Pharmacy, Tumkur, affiliated to RGUHS, Bangalore.*

²3rd Year Pharm D, Department of Pharmacy Practice, Akshaya Institute of Pharmacy, Tumkur, affiliated to RGUHS, Bangalore.

Corresponding author:

Dr. Shivaraj D R

Email: Shivaraj.dr27@gmail.com

ORCID: 0000-0002-9284-4360

ABSTRACT

Rifampicin remains the backbone of curative short-course therapy for drug-susceptible tuberculosis, yet the same property that makes it indispensable as an antimycobacterial, sustained activation of the pregnane X receptor, makes it the most consequential enzyme inducer in routine clinical use. Full induction of hepatic and intestinal cytochrome P450 enzymes and of P-glycoprotein develops over roughly a week and dissipates over about two weeks after the drug is stopped, so the interaction burden is present for the entire six-month regimen and for a transitional fortnight on either side of it. This

review sets out the molecular basis of that induction, then works through the drug classes where the clinical stakes are highest: antiretrovirals, oral anticoagulants, hormonal contraceptives, calcineurin inhibitors in transplant recipients, oral antidiabetic agents, statins, and the newer anti-tuberculosis agents used in drug-resistant disease. For each class the question is not whether an interaction exists but what to do about it, and the available answers fall into a small set of recurring strategies: substitute rifabutin where its weaker induction is tolerable, escalate the dose of the victim drug under measured monitoring, switch to a method or molecule that does not depend on the induced pathway, or defer a non-essential drug until induction has resolved. The final section translates these strategies into decision support suited to settings that carry most of the world's tuberculosis and the least laboratory capacity, where therapeutic drug monitoring is scarce and the prescriber at the point of care is often not the one who started the interacting drug. The weight of evidence supports a structured, anticipatory approach built around the induction time course rather than reactive dose chasing.



Keywords

Rifampicin; Drug interactions; Pregnane X receptor; Cytochrome P450 CYP3A4; Tuberculosis; Antiretroviral agents; Rifabutin; Therapeutic drug monitoring

1. Introduction

Tuberculosis returned to its position as the leading cause of death from a single infectious agent in the most recent global accounting, with an estimated 10.8 million people falling ill in 2023 and an incidence of 134 per 100 000 population ¹. People living with HIV accounted for 6.1% of those cases, some 662 000 individuals, and it is precisely this group that carries the heaviest interaction burden because effective antiretroviral therapy must run alongside tuberculosis treatment ¹. The standard six-month regimen for drug-susceptible disease is built on rifampicin, and no equally short, equally effective regimen that omits a rifamycin has displaced it for routine use ². Any serious attempt to manage the co-treated patient therefore has to manage rifampicin.

The difficulty is that rifampicin does not simply undergo metabolism alongside the drugs it accompanies; it reprograms the body's capacity to clear them. Within days of the first dose it increases the expression of the enzymes and transporters that eliminate a large fraction of orally administered medicines, and it does so broadly rather than selectively. A patient who begins tuberculosis treatment while taking a calcineurin inhibitor, a direct oral anticoagulant, or a boosted protease inhibitor can lose

therapeutic exposure to that drug within the first week, often before anyone has thought to check. The clinical consequences range from the inconvenient to the catastrophic: breakthrough seizures, graft rejection, thromboembolism, unintended pregnancy, and loss of virological control have all been documented as direct results of rifampicin-driven induction.

What makes this a tractable problem rather than an open-ended hazard is that the mechanism is singular and well characterised. Almost all of rifampicin's clinically important interactions trace back to one receptor and a predictable downstream response, which means the interactions can be anticipated from first principles rather than memorised case by case. A prescriber who understands that rifampicin will lower the exposure of a CYP3A4 substrate by a large and roughly knowable amount, on a defined timeline, is in a far better position than one who treats each new co-medication as a surprise.

Three features of the problem shape everything that follows. First, the induction has a time course, and that time course is as important as its magnitude: it governs when a dose increase should begin, when it becomes dangerous to continue, and how long caution must persist after rifampicin stops ^{3,4}. Second, the strategies for managing an interaction are few and transferable, so a clinician who has learned to manage the rifampicin-tacrolimus interaction already understands most of what is needed for rifampicin and sirolimus. Third, the places where co-treatment is most common are the places



where the monitoring tools taken for granted in well-resourced settings are least available, which means the guidance that matters most is guidance that works without a drug assay.

This review is organised around those three features. It first establishes the mechanistic basis of induction in enough detail to make the interactions predictable, with attention to the often-overlooked distinction between induction and the transient transporter inhibition seen with the first dose. It then addresses management class by class, concentrated on the drug groups where co-administration is frequent and the margin for error is small. It closes with a decision-support framework intended for high-burden, low-resource settings, where the right default matters more than the ideal individualised plan.

2. Mechanistic basis of rifampicin-mediated induction

2.1 The pregnane X receptor as master switch

Rifampicin is a high-affinity agonist of the pregnane X receptor (PXR, NR1I2), a ligand-activated transcription factor expressed most abundantly in hepatocytes and enterocytes³. On binding rifampicin, PXR heterodimerises with the retinoid X receptor and the complex docks onto response elements in the promoter and enhancer regions of its target genes, including an everted repeat separated by six base pairs in the CYP3A4 upstream region³. Transcription of those genes rises, more enzyme and transporter protein is produced, and the metabolic and efflux capacity of liver and gut increases accordingly.

The constitutive androstane receptor contributes to the same programme and shows considerable cross-talk with PXR, which is why the set of genes rifampicin induces overlaps with the set induced by phenobarbital and several antiepileptics³.

The breadth of the PXR response is the reason rifampicin interacts with so many drugs. A single activated receptor drives the coordinated up-regulation of CYP3A4, CYP2C9, CYP2C19, CYP2B6, several UDP-glucuronosyltransferases, and the efflux transporter P-glycoprotein³. Because CYP3A4 alone participates in the metabolism of a large share of marketed drugs, and because P-glycoprotein governs the intestinal absorption and biliary and renal excretion of many others, the induced state touches an unusually wide pharmacological territory.

2.2 Which pathways are induced, and by how much

CYP3A4 is the most strongly and most efficiently induced of the enzymes. In primary human hepatocytes, exposure to rifampicin raised CYP3A4 messenger RNA roughly 14-fold, with about a 10-fold spread between individuals, a variability that foreshadows the clinical observation that some patients lose almost all exposure to a sensitive substrate while others are affected less³. The consequences for orally administered CYP3A4 substrates are severe because the drug is exposed to induced enzyme twice, once in the gut wall during absorption and again in the liver during first pass. Simvastatin exposure fell by about 87%



under rifampicin, and prednisolone clearance rose by 45% with a 66% fall in exposure, both figures illustrating the scale of effect on sensitive oral substrates³.

The other enzymes are induced to a smaller but still clinically relevant degree. CYP2C9 induction underlies the warfarin interaction, where the effect on anticoagulant requirement is large and slow to develop. CYP2B6 messenger RNA rose about 2.1-fold in hepatocytes, which matters for efavirenz, a predominantly CYP2B6-cleared antiretroviral³. Glucuronidation capacity rises as well, through induction of UGT1A enzymes, and this is the pathway responsible for

the loss of exposure to dolutegravir and to several other glucuronidated drugs³.

P-glycoprotein deserves separate emphasis because its induction is independent of any effect on metabolism. After a course of rifampicin, intestinal P-glycoprotein content in healthy volunteers rose about 3.5-fold, with a parallel rise in messenger RNA after 600 mg daily for nine days³. For a drug that is a P-glycoprotein substrate but not appreciably metabolised, such as digoxin, this transporter induction is the whole of the interaction, and it will be missed by any mental model that equates rifampicin interactions with cytochrome P450 alone.

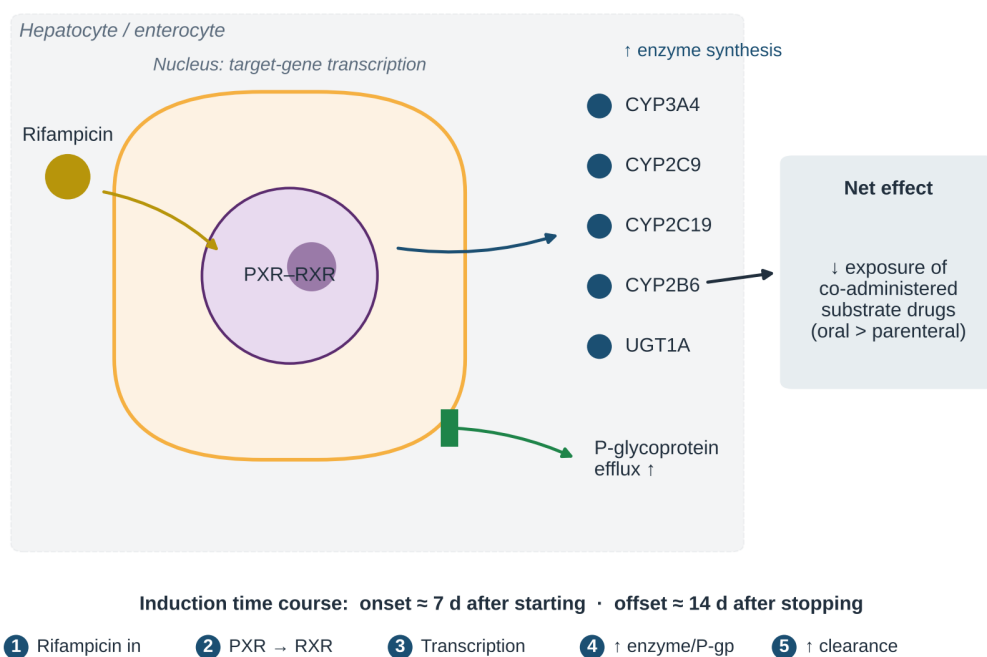


Figure 1. Rifampicin drives broad, PXR-mediated induction of drug-metabolising enzymes and efflux transport. On entering the hepatocyte or enterocyte, rifampicin activates the pregnane X receptor (PXR), which heterodimerises with the retinoid X receptor (RXR); the dimer increases transcription of CYP3A4, CYP2C9, CYP2C19, CYP2B6 and the UGT1A glucuronosyltransferases, and of the efflux transporter P-glycoprotein, so the clearance of co-administered substrate drugs rises.



2.3 The time course, and why it dictates management

Induction is a transcriptional process, so it is neither immediate nor instantly reversible. New enzyme and transporter protein must be synthesised before clearance rises, and existing protein must turn over before clearance falls again. In practical terms, induction reaches its maximum about one week after rifampicin is started and wears off over roughly two weeks after it is stopped ⁴. These two intervals are the hinges on which safe management turns.

The onset interval means that a victim drug started at the same time as rifampicin will show falling concentrations across the first week, so a patient can appear stable at day two and be subtherapeutic at day ten. The offset interval is the more dangerous of the two. A patient whose victim-drug dose was escalated to overcome induction, for example a transplant recipient on a tripled tacrolimus dose, will experience a return of normal clearance over the two weeks after rifampicin stops, and unless the escalated dose is brought back down on the same schedule the drug will accumulate to toxic concentrations. The rifampicin-tacrolimus literature contains exactly this sequence, with trough concentrations falling again within days of a dose being reduced after rifampicin withdrawal, which is simply the offset running in the opposite direction ⁵. Any management plan that raises a dose during co-treatment is incomplete unless it also specifies the taper after rifampicin ends.

2.4 Induction is not the whole story: transient transporter inhibition

A mechanistic account that stops at induction will mispredict a small but important set of interactions. On first exposure, before induction has developed, rifampicin acts as an inhibitor of the hepatic uptake transporters of the organic anion transporting polypeptide family, particularly OATP1B1. For drugs that depend on OATP1B1 for hepatic uptake, the first rifampicin doses can transiently raise, not lower, their plasma concentrations. The pravastatin data make the point: rifampicin reduced pravastatin exposure by about 31% overall, a far smaller effect than for simvastatin, and without any change in peak concentration or half-life, a pattern more consistent with modest transporter-level effects than with the wholesale metabolic induction seen with CYP3A4 substrates ⁶. The clinical implication is narrow but real. For a handful of transporter substrates the direction of the interaction depends on whether rifampicin has been given once or chronically, and single-dose interaction data on such drugs cannot be extrapolated to steady-state co-treatment.

2.5 Does higher-dose rifampicin induce more?

Programmes aiming to shorten tuberculosis treatment have tested rifampicin doses well above the standard 10 mg/kg, which raises a reasonable worry that the interaction burden might worsen in proportion. The best direct evidence is reassuring. In adults with pulmonary tuberculosis given a validated probe cocktail, raising the rifampicin dose from 10 to 40 mg/kg produced only modest further induction of most



pathways: the geometric mean ratios for high versus standard dose were 80% for the CYP2C9 probe tolbutamide, 55% for the CYP2C19 probe omeprazole, 77% for the CYP2D6 probe dextromethorphan, and 62% for the CYP3A probe midazolam, while the CYP1A2 probe caffeine showed no additional effect⁷. These added decrements are small against the backdrop of the roughly 90% or greater reductions that standard-dose rifampicin already produces for sensitive substrates such as midazolam and omeprazole⁷. The investigators concluded that management recommendations developed for standard-dose rifampicin can largely carry over to high-dose regimens, with the caveat that narrow-therapeutic-index CYP3A or CYP2C19 substrates, and fixed-dose oral CYP3A substrates such as dexamethasone in tuberculous meningitis, may need closer attention at the higher dose, and that anything already contraindicated at standard dose stays contraindicated⁷.

3. A framework for anticipating interactions

Because the mechanism is singular, the interactions can be triaged before any reference table is opened. Three questions settle most

cases. Is the co-medication cleared mainly by a PXR-regulated pathway, chiefly CYP3A4, CYP2C9, CYP2C19, CYP2B6, UGT, or P-glycoprotein? Is it given orally, exposing it to induced gut-wall enzyme and first-pass liver, or parenterally, which blunts the effect? And does it have a narrow therapeutic index or a hard clinical endpoint, such as transplant rejection, thrombosis, pregnancy, or virological failure, where a large loss of exposure cannot be absorbed by physiological reserve? A drug that answers yes to all three is a high-stakes interaction that must be managed before rifampicin is started, not after a problem appears. A drug that answers no to the first question, for example one cleared by renal excretion of unchanged drug, can usually be left alone. This triage will not replace the class-specific detail that follows, but it correctly sorts the majority of co-medications and, more importantly, it flags the dangerous ones early enough to act.

4. Class-by-class management

Table 1 summarises the interactions treated below, with the pathway involved, the approximate size of the effect, the recommended response, and the source for each. The sections that follow give the reasoning behind each entry.

Table 1. Clinically important rifampicin interactions by drug class, with the induced pathway, the approximate effect on victim-drug exposure, and the recommended management. Abbreviations: AUC, area under the concentration-time curve; DOAC, direct oral anticoagulant; GMR, geometric mean ratio; INR, international normalised ratio; IUD, intrauterine device; PI, protease inhibitor; RIF, rifampicin; TDM, therapeutic drug monitoring; UGT, UDP-glucuronosyltransferase.

Drug or class	Main induced pathway	Approximate effect	Recommended management	Ref
Dolutegravir	UGT1A1, CYP3A4	Trough reduced (GMR 0.57 vs standard-dose RIF)	Increase to 50 mg twice daily during RIF and for 2 weeks after	8



Efavirenz	CYP2B6	Modest reduction	No change; standard dose remains effective	9
Lopinavir/ritonavir	CYP3A4	Large; not overcome at standard dose	Substitute rifabutin; or double-dose/super-boost (poorly tolerated)	9
Warfarin	CYP2C9, CYP3A4	Large loss of effect; +233% dose over 4 months still insufficient in one report	Frequent INR, anticipatory dose increase, planned reduction after RIF	3
DOACs (apixaban, rivaroxaban, dabigatran, edoxaban)	CYP3A4, P-glycoprotein	Reduced exposure, no bedside measure	Avoid; switch to INR-controlled warfarin or a parenteral agent	3
Hormonal contraceptives (pill, implant)	CYP3A4, UGT	Reduced hormone exposure; documented implant failure	Add barrier method or switch to copper IUD; continue 4 weeks after RIF	10
Tacrolimus, cyclosporine	CYP3A4/5, P-glycoprotein	Trough collapses within days; dose up 2 to 3-fold	TDM-guided increase then taper; consider rifabutin	5
Glimepiride	CYP2C9	AUC reduced 34%, half-life 25%	Monitor glucose; dose change usually unnecessary	11
Simvastatin	CYP3A4	Exposure reduced about 87%	Pause, or use a less CYP3A4-dependent statin	3
Pravastatin	Transporter-mediated	Exposure reduced about 31%	Usually tolerable; preferred statin if one is needed	6
Bedaquiline	CYP3A4	AUC reduced about 59% (steady state about 79%)	Do not co-administer	12

4.1 Antiretroviral agents

The HIV-tuberculosis co-treated patient is the archetypal interaction case, and the antiretroviral class shows every management strategy in use at once. The integrase inhibitor dolutegravir is cleared largely by UGT1A1 with a CYP3A4 contribution, both induced by rifampicin, and its exposure falls substantially during co-treatment. The established response is not to abandon the drug but to double its frequency, giving 50 mg twice daily rather than once daily for the duration of rifampicin-based treatment and for about two weeks afterward; the extra fortnight covers the

offset of induction⁸. This approach preserves virological control: in a study of co-treated adults, even with high-dose rifampicin that pushed dolutegravir troughs lower still, with a geometric mean ratio of 0.57 against standard-dose rifampicin, virological failure at week 24 was no different between groups, 14.9% versus 14.0%⁸. The twice-daily strategy is the template for the whole review, a dose increase matched to the induction time course and reversed on a defined schedule.

Efavirenz, cleared predominantly by CYP2B6, is affected more modestly and remains effective at



its standard dose with rifampicin, which is why it was long the preferred anchor for co-treated patients despite the induction of its own metabolism⁹. Nevirapine is a weaker option because starting it at the usual lead-in dose during rifampicin co-treatment leaves concentrations suboptimal, and it carries overlapping hepatotoxicity with the tuberculosis drugs⁹. The protease inhibitors are the hardest case. Rifampicin reduces lopinavir exposure to a degree that cannot be overcome at standard dose, and the two documented workarounds, super-boosting with additional ritonavir or doubling the lopinavir-ritonavir dose, are poorly tolerated and only partly effective, so the preferred route for a patient who needs a protease inhibitor is to substitute rifabutin for rifampicin rather than to manipulate the antiretroviral⁹. Raltegravir falls between these; it retains activity only at increased doses and only in patients with a lower baseline viral load⁹. The pattern across the class is instructive: where the victim drug has dosing flexibility, as dolutegravir does, the interaction is managed by escalation; where it does not, as with the protease inhibitors, the inducer itself is swapped.

4.2 Oral anticoagulants

Anticoagulation during rifampicin therapy is dangerous in both directions and easy to get wrong. Warfarin is cleared by CYP2C9 and CYP3A4, both induced, and the loss of anticoagulant effect is among the largest and slowest of all rifampicin interactions. The dose requirement can rise severalfold, and in one account a 233% increase sustained over four

months was still insufficient to restore the target effect, a reflection of how completely induction can overwhelm a CYP2C9 substrate³. Two hazards follow. During co-treatment, a patient whose dose is not aggressively raised is under-anticoagulated and at thromboembolic risk. After rifampicin stops, a patient left on the elevated dose is dangerously over-anticoagulated as CYP2C9 activity returns over two weeks. Management requires frequent international normalised ratio monitoring from the first week, anticipatory upward titration during co-treatment, and a planned reduction tracking the offset once rifampicin ends.

The direct oral anticoagulants are a different problem with a simpler answer. Apixaban, rivaroxaban, dabigatran, and edoxaban are substrates of P-glycoprotein, and the first three also of CYP3A4 to varying degrees, so rifampicin reduces their exposure through combined transporter and enzyme induction. Unlike warfarin, these agents offer no measurable effect to titrate against at the bedside, so a prescriber cannot confirm that a dose increase has restored protection. For that reason the combination is best avoided altogether, with a switch to warfarin under international normalised ratio control, or to a parenteral anticoagulant, for any patient who genuinely requires anticoagulation during rifampicin therapy. The absence of a monitoring assay, not the magnitude of the interaction alone, is what makes the direct oral anticoagulants unsuitable here.



4.3 Hormonal contraceptives

Rifampicin reduces the efficacy of systemic hormonal contraception by inducing the metabolism and glucuronidation of both the estrogen and progestogen components, and the failures are not theoretical. A woman who conceived while using a subdermal etonogestrel implant during rifampicin-based tuberculosis treatment is a documented and foreseeable outcome, the implant's steady low progestogen output being exactly the kind of exposure that induction can push below the ovulation-suppressing threshold¹⁰. Combined oral contraceptives, progestogen-only pills, and subdermal implants are all affected. The guidance from the major eligibility frameworks is consistent: women who need long-term rifampicin should not rely on these methods alone, and should either add a barrier method or, preferably, switch to a method that does not depend on hepatic clearance of a circulating hormone¹⁰.

The methods that remain reliable are those whose action is local or independent of induced metabolism. The copper intrauterine device is unaffected because it has no hormonal component. The levonorgestrel intrauterine system acts primarily on the endometrium at the site of release and is generally considered to retain efficacy. Depot medroxyprogesterone acetate, given by injection at a dose far above the ovulation-suppression threshold, is usually regarded as retaining efficacy, though the conservative course where any doubt exists is to favour an intrauterine method. The practical

message for services that treat large numbers of women of reproductive age is to raise contraception at the start of tuberculosis treatment as a routine step, not to wait for the patient to ask, and to extend the additional precautions for about four weeks beyond the last rifampicin dose to cover the offset of induction.

4.4 Calcineurin inhibitors and transplant immunosuppression

In transplant recipients the rifampicin interaction is potentially graft-ending. Tacrolimus and cyclosporine are CYP3A4 and CYP3A5 substrates and P-glycoprotein substrates, so induction attacks both their metabolism and their absorption, and trough concentrations can collapse within days of starting rifampicin. A renal transplant recipient required a tacrolimus dose increase from 4 to 9 mg daily, slightly more than doubling, to restore troughs after rifampicin was added, with the trough falling from 6.1 to 3.7 ng/mL within about four days of the first rifampicin dose⁵. Cyclosporine shows the same pattern, with dose requirements rising roughly threefold to maintain therapeutic concentrations³. The offset is as treacherous as the onset. In the same tacrolimus case the trough fell again after rifampicin was stopped and the dose reduced, which shows that the return of normal clearance has to be tracked just as carefully as its loss⁵.

Management here depends absolutely on therapeutic drug monitoring, which makes this one of the few interactions that cannot be managed safely by protocol alone. Where frequent trough measurement is available, the calcineurin inhibitor dose is titrated upward



against target during co-treatment and tapered against target afterward. Where a rifamycin is clinically avoidable, many transplant programmes prefer a non-rifamycin regimen or substitute rifabutin precisely because the monitoring demands of full-dose rifampicin are so heavy. The case reports in this area are valuable less for their exact dose figures, which vary with CYP3A5 genotype and co-medication, than for their consistent demonstration that the effect is large, rapid, sustained, and fully reversible on the induction timeline ⁵.

4.5 Oral antidiabetic agents

The antidiabetic interactions are generally milder and are a useful counterweight to the alarming examples, because they show that not every rifampicin interaction demands intervention. Glimepiride, a CYP2C9-metabolised sulfonylurea, had its exposure reduced by about 34% and its half-life shortened by about 25% under rifampicin, yet the blood-glucose-lowering effect was not significantly diminished in healthy volunteers ¹¹. The sensible reading is that the interaction is real but usually absorbable, so it calls for attention to glycaemic control rather than a reflexive dose change. Other oral agents vary. The meglitinide repaglinide, a CYP2C8 and CYP3A4 substrate, loses exposure more substantially, and short-acting insulin secretagogues can require dose adjustment guided by glucose monitoring. Metformin, cleared renally as unchanged drug through organic cation transporters rather than by any PXR-regulated enzyme, is not meaningfully induced and is a reasonable anchor agent during

co-treatment. The general approach is pragmatic: intensify glucose self-monitoring when rifampicin starts, adjust the oral agent to the measured response, and reverse any change as induction resolves, with the reassurance that this class rarely produces a dangerous loss of control on its own.

4.6 Statins and cardiovascular drugs

The statins divide sharply according to how heavily they depend on CYP3A4 and on OATP1B1 uptake. Simvastatin, extensively metabolised by CYP3A4, is among the most severely affected of all rifampicin victim drugs, with exposure cut by about 87%, which abolishes most of its lipid-lowering benefit during co-treatment ³. Atorvastatin and lovastatin are affected similarly in direction if less in degree. Pravastatin, which is not appreciably CYP3A4-metabolised and depends on transporter-mediated disposition, loses only about 31% of its exposure and shows no change in peak concentration or half-life, a far more tolerable interaction ⁶. The practical consequence is that where lipid lowering must continue through tuberculosis treatment, a less CYP3A4-dependent statin is preferable to a dose increase of simvastatin, which cannot realistically be escalated enough to compensate. For most patients, however, statin therapy is preventive and can simply be paused or left at a nominal dose through a six-month course and resumed at full effect afterward, which avoids the interaction entirely. Among other cardiovascular agents, the P-glycoprotein substrate digoxin loses exposure through transporter induction alone and warrants



concentration monitoring, while several calcium-channel and antiarrhythmic CYP3A4 substrates lose substantial effect and may need alternative agents.

4.7 Opioids, antiepileptics, corticosteroids and azole antifungals

Several further classes recur often enough in co-treated patients to warrant brief, specific treatment. Methadone is a CYP3A4 and CYP2B6 substrate, and rifampicin can precipitate opioid withdrawal by lowering its concentration, so patients on opioid substitution therapy need anticipatory upward titration of the methadone dose when rifampicin starts and a reduction when it stops, both guided by withdrawal symptoms rather than by assay ⁴. Antiepileptic drugs cut both ways. Phenytoin and carbamazepine are themselves inducers and are CYP-metabolised, and the net effect of combining them with rifampicin is unpredictable enough that concentration monitoring is advisable where seizures are a risk; valproate, differently handled, is a steadier companion. Corticosteroids are meaningfully induced, with prednisolone exposure falling by about two-thirds, which matters most when a glucocorticoid is doing essential work, as dexamethasone does in tuberculous meningitis, where the induced loss of exposure may justify a higher corticosteroid dose ³. The azole antifungals are a two-way problem: rifampicin sharply lowers the concentrations of itraconazole, ketoconazole, and to a lesser extent fluconazole and voriconazole, undermining antifungal efficacy, while the azoles in turn inhibit rifampicin-independent pathways,

so co-administration of rifampicin with itraconazole or voriconazole is generally avoided in favour of an alternative antifungal or, where feasible, rifabutin.

4.8 Second-line and novel anti-tuberculosis agents in drug-resistant disease

A particularly important interaction sits inside tuberculosis therapy itself. Bedaquiline, a cornerstone of modern all-oral regimens for rifampicin-resistant and multidrug-resistant tuberculosis, is metabolised by CYP3A4, and rifamycins induce its clearance heavily. Rifampicin reduced bedaquiline exposure by about 59% over a two-week assessment, and population modelling projected the steady-state reduction at closer to 79%, with clearance increased almost fivefold ¹². Because this loss cannot be reliably overcome by dose escalation and a higher bedaquiline dose would raise early peak concentrations of the active metabolite with uncertain safety, the recommendation is unambiguous: rifampicin and bedaquiline should not be co-administered ¹². In practice this rarely forces a conflict, because a patient with rifampicin-resistant disease should not be receiving rifampicin in the first place, but the interaction becomes a live hazard whenever a drug-resistant diagnosis is delayed and a patient is started empirically on a rifampicin-based regimen that must then be switched. It also stands as the clearest illustration of the review's central point, that the induction mechanism is powerful enough to defeat even an essential drug, and that recognising this before co-prescribing is the only safe course.



5. Decision support for high-burden settings

The settings that carry most of the world's tuberculosis share a set of constraints that reshape what good interaction management looks like. Therapeutic drug monitoring is often unavailable or slow, the clinician initiating tuberculosis treatment is frequently not the one managing the patient's other conditions, continuity of records is imperfect, and the patient may not know the names of the drugs they take for hypertension, contraception, or mental health. In such conditions the ideal of individualised, assay-guided dose adjustment is unattainable for most patients, and the practical goal becomes choosing defaults that are safe without monitoring. The following principles, drawn from the mechanisms and class data above, are intended to be usable at the point of care.

Take a structured medication history before the first rifampicin dose, not after. Because induction develops over the first week, the window to prevent harm is at initiation. A short checklist oriented to the high-stakes classes, anticoagulants, antiretrovirals, hormonal contraception, transplant immunosuppressants, antiepileptics, and opioid substitution, captures most of the dangerous interactions with a few direct questions, and it does so while there is still time to substitute or plan.

Prefer substitution of the inducer where a high-stakes interaction is unavoidable. Rifabutin is a weaker enzyme inducer than rifampicin while retaining antimycobacterial efficacy, and it is the established substitute when

a patient must continue a boosted protease inhibitor or a calcineurin inhibitor whose exposure rifampicin would decimate ⁹. Where rifabutin is available in the national programme, routing the most interaction-prone patients toward it is often simpler and safer than attempting to titrate the victim drug blind.

Where escalation is the chosen strategy, pre-specify both the increase and the taper. The dolutegravir model, 50 mg twice daily throughout rifampicin therapy and for two weeks after, is the paradigm: a fixed, evidence-based dose increase that needs no assay and a fixed stop date tied to the induction offset ⁸. The same logic applies to methadone and, where monitoring exists, to warfarin and calcineurin inhibitors. The single most common management error is to raise a dose during co-treatment and forget to lower it afterward, which converts an under-exposure problem into a toxicity problem over the two weeks after rifampicin stops. Any escalation order should carry its own expiry.

Switch the victim to a non-induced pathway when one exists. This is the lowest-maintenance strategy because it removes the interaction rather than compensating for it. A copper intrauterine device replaces an induced contraceptive hormone, metformin replaces an induced sulfonylurea where glycaemic targets allow, and a less CYP3A4-dependent statin replaces simvastatin. Each substitution converts a drug that needs vigilance into one that does not.

Defer the non-essential. Many co-medications, preventive statins among them, can simply be paused for the duration of a six-month course



and resumed afterward, which is safer than managing an interaction that confers little benefit over that interval.

These four strategies and the conditions that select among them are set out in Table 2. The

choice is rarely about the pharmacology alone; it turns on whether a monitoring assay is at hand and whether the victim drug can be dosed flexibly.

Table 2. The four management strategies for a rifampicin interaction, the circumstances that select each one, a representative example, and the main caveat. IUD, intrauterine device; PI, protease inhibitor.

Strategy	When it fits	Example	Main caveat
Substitute the inducer (rifabutin)	Victim drug lacks dosing flexibility and has a hard endpoint	Boosted PI; calcineurin inhibitor	Depends on rifabutin supply; still a weaker inducer, not an inert one
Escalate the victim dose with a matched taper	Victim has dosing flexibility and the effect is surmountable	Dolutegravir 50 mg twice daily; methadone	The taper over the two-week offset must be specified in advance
Switch to a non-induced pathway	A clinically adequate non-induced alternative exists	Copper IUD; metformin; pravastatin	The alternative must meet the same clinical goal
Defer the non-essential	The drug confers little benefit over a six-month course	Preventive statin	Only for genuinely deferrable therapy

Model-informed approaches have a growing place even where bedside assays do not. Physiologically based pharmacokinetic models reproduce the magnitude of rifampicin's CYP3A induction interactions reasonably well once the maximal induction parameter is calibrated against clinical probe data, and they can explore how a dosing schedule changes the size of an interaction without exposing a patient to the experiment¹³. Their current role is to inform the fixed-dose recommendations that programmes then deploy, the twice-daily dolutegravir rule being a downstream example of exactly this kind of reasoning. As these models are embedded in prescribing tools, they offer a route to bring individualised dosing logic to settings that will never have widespread therapeutic drug monitoring, provided the recommendations are

translated into simple, memorable defaults rather than left as outputs requiring interpretation.

Finally, the human system matters as much as the pharmacology. The transplant and warfarin case literature repeatedly credits active pharmacist involvement and structured monitoring with averting harm⁵. In high-burden programmes, embedding a brief interaction check into the directly observed therapy workflow, and giving the dispensing pharmacist or nurse an explicit mandate to flag the high-stakes classes, places a second set of eyes at the point where the inducer and the victim drug first meet. That organisational step is likely to prevent more harm at scale than any refinement of an individual dose.



6. Discussion

The weight of evidence supports a clear and somewhat liberating conclusion: rifampicin's interactions, for all their number and severity, are among the most predictable in pharmacology, and most can be managed well with a small repertoire of strategies applied on a known timeline. The predictability follows from the singular mechanism. One receptor, PXR, drives a coordinated induction of a defined set of enzymes and transporters, with a magnitude that is large but bounded and a time course that is consistent across drugs, about a week to onset and two weeks to offset^{3,4}. A clinician who holds those facts can anticipate the direction, the rough size, and above all the timing of almost any rifampicin interaction, which is a far stronger position than reactive management allows.

The evidence base nonetheless has real weaknesses that temper how firmly individual recommendations can be stated. Much of the quantitative data comes from small pharmacokinetic studies in healthy volunteers, whose induction response may differ from that of patients with active tuberculosis, HIV, malnutrition, or hepatic impairment, and whose numbers are too few to characterise the roughly 10-fold interindividual variability in CYP3A4 induction that the mechanistic work has shown to exist³. Several of the most clinically vivid interactions, including the contraceptive implant failure and the tacrolimus collapse, rest on case reports, which establish that an interaction can be dangerous but cannot quantify how often it is^{5,10}. Hard clinical endpoints are scarce: the co-treated

HIV studies that measured virological failure are a welcome exception, but for most interactions the published outcome is a change in drug concentration, and the leap from a lowered concentration to a clinical event is frequently assumed rather than demonstrated⁸. Where sources disagree they tend to do so on magnitude rather than direction, and the direction is almost always the one the mechanism predicts, which is itself a form of corroboration.

Three gaps are worth naming because they are addressable. The first is the near-total absence of interaction data generated in the populations and settings that actually carry the co-treatment burden, which leaves programmes extrapolating from volunteer studies conducted elsewhere. The second is the shortage of pragmatic trials testing whether a structured, fixed-default management strategy of the kind outlined here actually reduces adverse outcomes compared with usual care, as opposed to merely normalising drug concentrations. The third is the uneven availability of rifabutin, the single most useful substitution tool, across the national programmes that would benefit most from it. None of these is a scientific mystery; each is a matter of directing study and supply toward where the need is greatest.

7. Conclusion

Rifampicin will remain central to tuberculosis treatment for the foreseeable future, and the interaction burden it imposes is therefore a permanent feature of co-treatment rather than a transient inconvenience. The argument of this



review is that the burden is manageable precisely because the mechanism is singular: PXR-driven induction of a defined set of enzymes and transporters, developing over a week and resolving over two, produces interactions that can be anticipated rather than merely discovered. The strategies for managing them reduce to a short list, substitute the inducer, escalate the victim dose with a matched taper, switch to a non-induced pathway, or defer the non-essential, and the choice among them is usually dictated by whether a monitoring assay is available and whether the victim drug has dosing flexibility. For high-burden settings the priority is to convert this understanding into safe defaults that work without an assay, to take the medication history before the first dose rather than after the first failure, and to ensure that every dose escalation carries its own stop date. The most useful next step the field could take is a pragmatic trial of such a structured default strategy, conducted in the settings that carry the disease, with clinical outcomes as its endpoint rather than drug concentrations.

Declarations

Funding. None.

Conflicts of interest. None declared.

References

1. World Health Organization. Global tuberculosis report 2024. Geneva: World Health Organization; 2024.
2. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment: drug-susceptible tuberculosis treatment. Geneva: World Health Organization; 2022. ISBN 978-92-4-004812-6.
3. Chen J, Raymond K. Roles of rifampicin in drug-drug interactions: underlying molecular mechanisms involving the nuclear pregnane X receptor. *Ann Clin Microbiol Antimicrob*. 2006;5:3. doi:10.1186/1476-0711-5-3.
4. Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivistö KT. Pharmacokinetic interactions with rifampicin: clinical relevance. *Clin Pharmacokinet*. 2003;42(9):819-850. doi:10.2165/00003088-200342090-00003.
5. Naylor H, Robichaud J. Decreased tacrolimus levels after administration of rifampin to a patient with renal transplant. *Can J Hosp Pharm*. 2013;66(6):388-392.
6. Kyrklund C, Backman JT, Neuvonen M, Neuvonen PJ. Effect of rifampicin on pravastatin pharmacokinetics in healthy subjects. *Br J Clin Pharmacol*. 2004;57(2):181-187. doi:10.1046/j.1365-2125.2003.01972.x.
7. Stemkens R, de Jager V, Dawson R, Diacon AH, Narunsky K, Padayachee SD, et al. Drug interaction potential of high-dose rifampicin in patients with pulmonary tuberculosis. *Antimicrob Agents Chemother*. 2023;67(10):e00683-23. doi:10.1128/aac.00683-23.
8. Sekaggya-Wiltshire C, Nabisere R, Musaazi J, Otaalo B, Aber F, Alinaitwe L, et al.



Decreased dolutegravir and efavirenz concentrations with preserved virological suppression in patients with tuberculosis and human immunodeficiency virus receiving high-dose rifampicin. *Clin Infect Dis.* 2023;76(3):e910-e919.
doi:10.1093/cid/ciac585.

9. Centers for Disease Control and Prevention. Managing drug interactions in the treatment of HIV-related tuberculosis. Atlanta (GA): Centers for Disease Control and Prevention; 2013.
10. Tufa TH, Fessehaye A, Abubeker FA. Etonogestrel contraceptive implant failure in a woman taking rifampin: a case report. *Contracept Reprod Med.* 2022;7:5.
11. Niemi M, Kivistö KT, Backman JT, Neuvonen PJ. Effect of rifampicin on the pharmacokinetics and pharmacodynamics of glimepiride. *Br J Clin Pharmacol.* 2000;50(6):591-595. doi:10.1046/j.1365-2125.2000.00295.x.
12. Svensson EM, Murray S, Karlsson MO, Dooley KE. Rifampicin and rifapentine significantly reduce concentrations of bedaquiline, a new anti-TB drug. *J Antimicrob Chemother.* 2015;70(4):1106-1114. doi:10.1093/jac/dku504.
13. Almond LM, Mukadam S, et al. Prediction of drug-drug interactions arising from CYP3A induction using a physiologically based dynamic model. *Drug Metab Dispos.* 2016;44(6):821-832.
doi:10.1124/dmd.115.066845.