Pharmacokinetics and pharmacodynamics of drug interactions involving rifampicin, rifabutin and antimalarial drugs

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Malaria and tuberculosis (TB) are two major global diseases mostly affecting the developing countries. Their treatment is often complex because of the drugs used, multidrug resistance, drug interactions and logistic problems such as drug availability and access. Patients are treated for TB for a minimum of 6 months and may concomitantly develop and be treated for malaria, especially during the rainy season. Rifampicin, a standard component of combination regimens for treating TB, is a potent inducer of hepatic cytochrome and other metabolic enzymes and is able to influence the pharmacokinetics of many drugs. Rifabutin, another rifamycin used less frequently than rifampicin, can also interact with drugs metabolized through the hepatic cytochromes. The mechanisms of any interaction of rifamycins with drugs used in malaria are not well defined. To complicate matters, acute malaria also plays a role in the pharmacokinetics and pharmacodynamics of drugs (i.e. quinine). The aim of this paper is to review known and potential drug–drug interactions between rifampicin, rifabutin and antimalarial drugs.

Keywords: treatment of malaria, tuberculosis, pharmacology of antimalarial agents

Introduction

Malaria and tuberculosis (TB) are endemic diseases in many countries with limited resources and are frequently found at the same time. Together, they kill more than 3 million people each year.1 These diseases have a synergic negative effect on public health and are considered to be great barriers to economic development. The relationship of these diseases with HIV and the problems of drug resistance are major causes of concern, and they adversely affect morbidity and mortality.1

The co-existence of these two diseases leads to various concerns about their treatment. For several reasons, simultaneous malaria and TB treatment poses many challenges. One of these is the potential for drug–drug interactions between the most commonly used drugs. Rifampicin, a standard component of combination regimens for treating TB, is a potent inducer of hepatic metabolism and is able to influence the pharmacokinetics of several drugs. Rifabutin, another rifamycin used less frequently than rifampicin, can also interact with drugs metabolized through the hepatic cytochromes. The drug–drug interactions of rifamycins with drugs used in malaria are not well defined. Moreover, acute malaria itself can influence the pharmacokinetics and pharmacodynamics of different drugs by influencing liver metabolism, binding to plasma proteins and excretion by mechanisms that remain unclear.2

The aim of this paper is to review known and potential drug–drug interactions between rifampicin, rifabutin and antimalarial agents.

Pharmacokinetics, pharmacodynamics and drug interactions

Pharmacokinetics studies the absorption, distribution, metabolism and excretion of a drug, and pharmacodynamics studies the relationship between the drug and its receptors, its mechanism of action and therapeutic effect. Both can play a role in drug–drug interactions.

Many drugs share the same metabolic pathways or target the same receptors. This leads to the occurrence of pharmacokinetic and pharmacodynamic differences, respectively. Drug–drug interactions occur mainly during drug absorption, distribution (plasma drug binding protein), biotransformation and excretion.

Most drugs are given by the oral route. Subsequently, absorption is mostly through the intestinal mucosa (duodenum). Drug bioavailability is dependent on an enterocyte P-glycoprotein, which can actively pump back drugs into the intestinal lumen, and on enterocyte cytochrome P450 (CYP450) enzymes, metabolizing the drug before it reaches the systemic circulation.3
Induction or inhibition of P-glycoprotein and enterocyte CYP450 can thus influence drug bioavailability. After being absorbed, drugs generally bind to plasma transport proteins (i.e. albumin, α-1-acid-glycoprotein). The level of binding protein plays a fundamental role in distribution and various drugs can affect protein binding. When the drug passes through the liver, it is metabolized to active and/or non-active metabolites. This is called biotransformation and this has a great influence on therapeutic efficacy. Drug biotransformation is dependent on several phases. Phase I consists of hydrolysis, oxidation and reduction, which is mediated mostly by CYP450. Phase II consists of conjugation and is mediated by enzymes such as uridine diphosphoglucuronosyl transferase, N-acetyl transferase and glutathione S-transferase. These enzymes play an important role in the detoxification and/or excretion rate of xenobiotics. Phase III is mediated by drug plasma membrane transporters (influx and efflux), such as P-glycoprotein, multi-drug resistance protein (MRP) and organic anion transport protein 2 (OATP2), that are localized in the liver on the endothelium and epithelium membrane, as well as in the gastrointestinal tract, kidney and other organs. They play an important role in drug pharmacokinetics and pharmacodynamics. In the liver, OATP1 and OATP2 are localized in sinusoidal phase membrane of hepatocytes and are responsible for the uptake of many drugs to be metabolized. MRP2 and P-glycoprotein are localized in the canalicular phase membrane of the hepatocytes and are responsible for pumping out xenobiotics (i.e. drugs and their metabolites) to the biliary canals. Since they are present in several types of cells, and mediate cell exposure to drugs, they can influence not only absorption, distribution, metabolism and elimination, but also drug concentrations inside the target cell and affect the therapeutic efficacy.

Acute malaria itself has been shown to influence the metabolism and distribution of certain drugs not, it seems, by influencing drug absorption but by increasing binding to α-1-glycoprotein in plasma. Inhibition of hepatic metabolism, mainly CYP3A4 enzymes in acute malaria, leads to a reduced clearance of quinine.

Rifampicin and rifabutin pharmacokinetics

Both rifampicin and rifabutin are drugs used for the treatment of TB. Rifampicin is derived from rifampicin B that is produced by Streptomyces mediterranei and has been in use since 1965. Rifabutin is derived from rifamycin S and is mostly used in HIV co-infected patients because it has fewer drug interactions with antiretroviral agents (i.e. protease inhibitors) than rifampicin. It is also used in atypical mycobacterial infections and, in some cases, it has been shown to be active when there is rifamycin resistance. Both drugs act by inhibiting the β-subunit-dependent DNA–RNA polymerase that leads to suppression of DNA formation by Mycobacterium tuberculosis. They are bactericidal and bacteriostatic and act intra- and extracellularly.

Absorption

Both drugs are generally well absorbed by the oral route. Altered absorption, however, has been observed in patients with AIDS, diabetes and gastrointestinal diseases. Furthermore, pharmacokinetic studies show a high inter-individual variability of rifampicin absorption characterized by slow and fast absorption patterns.

Distribution

Rifampicin is highly lipophilic, it is 80% bound to plasma proteins, mainly α-1-acid-glycoprotein, and it is characterized by a plasma half-life of 2–5 h. Rifabutin is 85% bound to plasma proteins in a concentration-independent manner. Due to their high lipophilicity, both demonstrate a high propensity for distribution and intracellular tissue uptake.

Biotransformation

Rifampicin is deacetylated by hepatic microsomal enzymes, and it is also a great CYP450 inducer, the most potent inducer of all drugs used in clinical practice. This leads to decreased drug concentrations by an autoinduction mechanism, whereby the drug stimulates its own metabolism into inactive metabolites.

Excretion

Rifampicin is rapidly eliminated mainly in the bile. Up to 30% is excreted in urine. Rifabutin is mostly excreted in urine, primarily as metabolites. About 30% of the dose is excreted in the faeces.

Enzyme induction and inhibition

Because of the influence on the liver metabolic activity, rifampicin has been shown to be involved in several drug–drug interactions.

Rifampicin is an N-acetyltransferase inhibitor and leads to a decrease in the acetylation ratio in fast acetylators. However, the most important mechanism behind rifampicin drug interactions is its potent inducing effect on hepatic and intestinal CYP450 enzyme activity (CYP3A4, CYP1A2, CYP2C9, CYP2C8 and CYP2C18/19). It undergoes progressive enterohepatic circulation and deacetylation to the primary active metabolite, 25-desacetyl-rifampicin.

Rifabutin is metabolized by CYP3A. Of the five metabolites that have been identified, 25-O-desacetyl and 31-hydroxy are the most predominant. The former has an activity equal to the parent drug and contributes up to 10% of the total antimicrobial activity.

Moreover, rifampicin has an important role in hepatic drug uptake and gastrointestinal absorption of drugs as it is a P-glycoprotein, an MRP, a transport system inducer and an OATP2 inhibitor. Based on tissue distribution of these membrane transporters, modulation of their activity may result in significant alterations in the pharmacokinetics and, potentially, the pharmacodynamics of several drugs.

The mechanism of rifampicin induction of CYP enzymes is mediated by the activation of nuclear pregnane X receptor (PXR), a member of the nuclear receptor superfamily. A recent study performed in mice demonstrated that CYP3A4 is dysregulated in PXR-null mice, confirming that PXR transcriptionally regulates CYP3A4. PXR binds to CYP3A promoters to activate reporter genes. PXR also up-regulates other Phase I, II and III enzyme genes, such as MDR1, a gene encoding
P-glycoprotein. Rifampicin is a PXR ligand and activates transcription of CYP3A4 and other proteins such as P-glycoprotein.

Another receptor, constitutive androstane receptor (CAR), is also involved in CYP3A4 transcriptional regulation, but rifampicin has a lesser effect on CAR than on PXR.

Rifampicin is responsible for broad changes in the pattern of gene expression, rather than increased expression of a small number of metabolic enzymes. Clinicians should be alert to the possibility of its multiple effects.23

Rifabutin induces CYP3A and may reduce the plasma concentrations of drugs that are mostly metabolized by this enzyme. However, rifabutin is a weaker enzyme inducer than rifampicin.24 Importantly, rifabutin is also a substrate of CYP3A4. Therefore, its concentrations may be altered during co-administration with CYP3A4 inducers and inhibitors and dose adjustments may be required.

Antimalarial drugs

Malaria treatment is far from simple. Resistance to chloroquine is widespread, and resistance to other agents and multidrug resistance is emerging in many countries.

There are 1500–2000 cases of imported malaria reported in the UK each year and 10–20 deaths. Approximately three-quarters of reported malaria cases in the UK are caused by Plasmodium falciparum.25 In 2002, 1337 cases of malaria were reported in the USA; all but five were imported.26 The success of malaria treatment is dependent on knowledge of the current malaria resistance patterns of the areas where the patient was infected.

Quinine

Quinine is one of the most commonly used drugs for malaria treatment worldwide. It is the first-line treatment for P. falciparum uncomplicated malaria and is a treatment option for P. falciparum complicated malaria in chloroquine-resistant regions.25–27 Quinine seems to act against Plasmodium spp. by inhibiting haem polymerase that leads to toxic haem levels.25 Quinine metabolism is interesting because acute malaria influences absorption, the binding-protein fraction, CYP450 activity and excretion of quinine. Pukrittayakamee et al.9 studied patients with severe malaria to assess the factors that could influence the decreased clearance of quinine and concluded that the most important factor was the impairment of CYP3A function.

Biotransformation. In acute malaria, 78% to 95% of quinine is bound to α-1-acid-glycoprotein.2 It is metabolized almost exclusively via CYP450, mostly by CYP3A4,28 and CYP2C19. The metabolism of quinine is not completely understood but CYP1A2 and CYP2D6 may also have a role.29,30 One of its metabolites is 3-hydroxyquinine, which is important as it has 10% of the activity of the parent drug.29

Excretion. Quinine is mostly eliminated via the hepatic route, and 20% of it is excreted unchanged in the urine.

Enzyme induction and inhibition. Quinine inhibits the activity of CYP2D631 and inhibits P-glycoprotein32 and biliary excretion. Therefore, it has an important role in the elimination of several drugs.

Drug interactions. There is evidence that rifampicin may have antimalarial activity in humans.33,34 The antimalarial mechanism of rifampicin may be similar to that observed in TB. The target of rifampicin may be the Plasmodium organellar circular DNA molecule that encodes the β-subunit of a prokaryocyte-like RNA polymerase.29,35

Both quinine and rifampicin influence several steps in drug metabolism and distribution.

Enterocyte P-glycoprotein activity is inhibited by quinine and induced by rifampicin.3 Rifampicin also induces enterocyte CYP3A. Overall, in theory, this could lead to a decrease in bioavailability of quinine.

In plasma, both rifampicin and quinine are bound to α-1-acid-glycoprotein. Acute malaria, TB14 and rifampicin administration16 increase α-1-acid-glycoprotein levels, and this could influence quinine distribution, metabolism and efficacy.

The OATP system is responsible for quinine hepatic uptake and rifampicin is an OATP inhibitor27,38 and could therefore theoretically influence quinine concentrations. Moreover, by inhibiting P-glycoprotein, quinine inhibits biliary excretion1 and may theoretically alter rifampicin half-life.

Several in vivo studies have been performed to investigate the interactions between quinine and rifampicin. Wanwimolruk et al.27 studied the effect of 1 week pre-treatment with rifampicin (and isoniazid) on quinine pharmacokinetics in healthy volunteers. They showed that the mean clearance of quinine was significantly greater (0.87 versus 0.14 L/h/kg) and the mean elimination half-life of quinine was shorter with rifampicin pre-treatment than when quinine was given alone (5.5 versus 11.1 h).

Pukrittayakamee et al.29 studied the effect of combined therapy (rifampicin and quinine) in patients with acute uncomplicated P. falciparum malaria. Interestingly, they observed that the parasite clearance was faster with the combination. This could be because of the rifampicin antimalarial effect rather than a drug interaction as rifampicin can take several days to induce CYP3A4 activity that is responsible for quinine metabolism. After the second day of rifampicin treatment, quinine pre-dose plasma concentrations decreased progressively throughout the treatment period, leading to a fall in quinine activity that may have been the reason for a malaria recrudescence rate five times higher in this group. The authors concluded that, although rifampicin could have therapeutic effects in malaria, the drugs should not be combined to treat malaria. In those patients who are already on rifampicin for the treatment of TB, quinine doses must be increased. However, no advice on dose-adjustment strategies has been provided and quinine therapeutic drug monitoring has been suggested to be useful to guide dosing.

Cerebral malaria is the commonest cause of non-traumatic encephalopathy in the world. The standard treatment is with quinine. Quinine penetrates relatively poorly into the cerebrospinal fluid (CSF) in patients with cerebral malaria, with a concentration approximately 2% to 7% of that measured in plasma. P-glycoprotein is one of the blood–brain barrier (BBB) membrane transporters and modulates central nervous system (CNS) drug exposure, playing an important role in preventing CNS drug accumulation. Reducing P-glycoprotein activity dramatically increases the penetration of many therapeutic drugs into
the CNS. Studies in rats have shown that brain capillary P-glycoprotein is transcriptionally up-regulated by the PXR, and as rifampicin is a PXR ligand, it increases P-glycoprotein expression in the BBB.\textsuperscript{38} Therefore, the co-administration of rifampicin and quinine could decrease quinine concentrations in the CSF. However, whether this compromises drug efficacy remains unclear, as the clinically relevant concentrations of quinine are those measured in the systemic circulation, where parasitized erythrocytes remain.

Despite being a less potent CYP3A4 inducer than rifampicin, rifabutin and quinine should also be cautiously co-administered as both drugs use the same metabolic pathways. Nevertheless, no data are available on the potential interaction between rifabutin and quinine.

**Chloroquine**

Despite the worldwide spread of \textit{P. falciparum} resistance to chloroquine, this drug is still used as a first-line treatment for \textit{Plasmodium ovale}, \textit{Plasmodium malariae} and \textit{Plasmodium vivax} in regions where there is no known resistance.

The mechanism of plasmodicidal action of chloroquine is not completely certain. It is thought to inhibit the haem polymerase of \textit{Plasmodium}, increasing haem to toxic levels. Chloroquine is almost completely absorbed when given by the oral route. It binds to plasma proteins, and it is metabolized in the liver by CYP450 (mainly CYP2C8 and CYP3A4/5)\textsuperscript{39} to desethylchloroquine, which has an activity similar to chloroquine, and bisdesethylchloroquine. The MRP membrane transport system is responsible for chloroquine cellular efflux and may be the mechanism implicated in the development of resistance to chloroquine. There are several in \textit{vitro} studies suggesting that \textit{P. falciparum} chloroquine resistance may be reversed with P-glycoprotein inhibitors such as roxithromycin\textsuperscript{40} or fluoxetine.\textsuperscript{41} Importantly, despite reporting that the observed effect occurred at clinically achievable concentrations, the difference in drug protein binding between the \textit{in vitro} and \textit{in vivo} systems may lead to remarkable differences between the two environments. Similar findings, however, have been observed both \textit{in vitro} and \textit{in vivo} with calcium channel blockers (i.e. verapamil). These showed effectiveness against chloroquine-resistant \textit{P. falciparum} by increasing chloroquine accumulation inside the food vacuole.\textsuperscript{32}

One study in infected mice reported that the combination of rifampicin and chloroquine decreased their survival rate and the rate of clearance of parasitaemia and increased the rate of recrudescence.\textsuperscript{43} The decrease in chloroquine efficacy when administered in combination with rifampicin may be due to the inducing effect of rifampicin on MRP\textsuperscript{20} and on CYP450 activity. Concomitant use of these drugs might have to be avoided; however, data in humans are lacking.

Studies are needed to explore drug–drug interactions between rifabutin and chloroquine as there are no data regarding this interaction.

**Atovaquone and proguanil**

Atovaquone, combined with proguanil, is a treatment option for \textit{P. vivax} infection. It is also used for malaria prophylaxis. Its activity against \textit{Plasmodium} is due to the inhibition of mitochondrial electron transport.\textsuperscript{27} Atovaquone is 99% bound to plasma proteins and has a 70 h half-life. It is characterized by an enterohepatic circulation, is metabolized in the liver and is mostly excreted unchanged in the faeces. There is \textit{in vitro} evidence of possible inhibition of CYP3A4 by atovaquone,\textsuperscript{44} and studies that used atovaquone in the treatment of \textit{Toxoplasma gondii} showed that atovaquone area under the curve (AUC) decreased remarkably (50%) when combined with rifampicin but not as much (34%) with rifabutin.\textsuperscript{44} The concomitant administration of atovaquone and rifampicin is therefore not recommended, while the clinical significance of the moderate decrease in atovaquone concentrations in the presence of rifabutin remains unclear.

Moreover, despite the lack of studies on rifabutin and atovaquone in malaria, there are several studies on their co-administration for the treatment of opportunistic infections. This combination seems to have a synergistic effect in the prophylaxis of \textit{Pneumocystis jiroveci} pneumonia and \textit{T. gondii} in mice.\textsuperscript{45}

Proguanil is used in combination with atovaquone and should not be used alone because resistance to it develops very quickly.\textsuperscript{27} Seventy-five percent of the drug is bound to plasma proteins, and it undergoes bioactivation by CYP2C19 to the active metabolite, cycloguanil. Cycloguanil inhibits plasmodial dihydrofolate reductase and influences DNA synthesis.

Since rifampicin is a potent inducer of CYP2C19, it is possible that it could affect proguanil antimalarial activity.

Data on this interaction are unavailable and further studies are needed to clarify the effect of rifampicin and rifabutin on proguanil pharmacokinetics and efficacy.

**Mefloquine**

Mefloquine is an antimalarial agent used for the treatment and prophylaxis of chloroquine-resistant \textit{P. falciparum} and non-falciparum malaria. It is also often used in combination with artemisinins. Its exact mechanism of action is not known. After absorption, it binds almost completely to plasma proteins and is metabolized by CYP3A into two inactive metabolites.\textsuperscript{46} It is known that the pharmacokinetics of mefloquine is altered in acute malaria.\textsuperscript{47}

Just like chloroquine, mefloquine resistance seems to be mediated by MDR transport system activity,\textsuperscript{48} which can be increased by rifampicin. Furthermore, rifampicin induces mefloquine metabolism,\textsuperscript{46} decreasing its AUC by 68% and half-life by 63%.\textsuperscript{49} Importantly, mefloquine metabolite AUC and clearance increased by 30% and 25%, respectively. These changes did not reach a statistical significance. The authors suggested avoiding simultaneous administration of mefloquine and rifampicin on the basis of these pharmacokinetic findings. However, no data are available on the clinical efficacy of this combination.

In 1999, Bermudez \textit{et al.}\textsuperscript{50} found that mefloquine has \textit{in vitro} and \textit{in vivo} activity against \textit{Mycobacterium avium} complex including strains with multidrug resistance. More studies are needed to further increase our knowledge about mefloquine pharmacodynamics and drug interactions with rifabutin and rifampicin.

**Artemisinins**

Artemisinins and their derivates (i.e. artemether and artesunate) are drugs recently developed to treat malaria. The advantages of these drugs are the antimalarial effect against \textit{P. falciparum}.
gametocytes (previously only susceptible to primaquine) and the lack of evidence of resistance to these agents to date.

Artemether did not prove to be better than quinine on survival rate, and artesunate is the first choice in low-transmission areas. These drugs should be given in combination therapy with other antimalarial agents (i.e. mefloquine) since better parasite clearance rates have been observed compared with monotherapy. High efficacy of two artemisinin-based combinations (artesunate plus amodiaquine and artemether plus lumefantrine) has been shown over the past few years in areas where TB is endemic.

The clinical pharmacology of artemisinin-based combination therapies is highly complex. All artemisinin compounds are metabolized by CYP3A4 to the active compound dihydroartemisinin, also available as a drug in itself. They also seem to induce CYP2C19 activity and their own metabolism. There are no studies looking at the concomitant administration of artemisinins and rifampicin or rifabutin. However, theoretically, drug interactions may occur because of the inducing effect of rifampicin and rifabutin on different CYP450 enzymes, leading to a more extensive time-dependent decline in drug plasma concentrations and hypothetical decrease in efficacy.

Amodiaquine and lumefantrine are metabolized by CYP2C8 and 3A4, respectively, and may be theoretically decreased by rifampicin or rifabutin co-administration. Pharmacokinetic/pharmacodynamic investigations to investigate the interaction between artemether/lumefantrine (Coartem®) and rifampicin are currently being conducted at the University of Makerere, Kampala, Uganda (clinicaltrials.gov NCT00620438; Dr Mohammed Lamorde, personal communication).

**Primmaquine**

Primmaquine is used to provide a cure for *P. vivax* and *P. ovale* malaria, and it is also gametocytocidal against *P. falciparum*. The mechanism of action is unknown. It is metabolized in the liver by CYP450 enzymes, possibly CYP3A4. Therefore, co-administration of primaquine and rifampicin or rifabutin may influence the pharmacokinetics of primaquine and alter its plasma concentration. However, there are no data on this potential interaction.

**Doxycycline and clindamycin**

Doxycycline is a tetracycline derivative that is used in malaria treatment in combination with quinine to ensure cure. It is an inhibitor of protein synthetase by disrupting messenger RNA and transfer RNA; 80% to 95% binds to plasma proteins and is metabolized in the liver by an unknown mechanism. No metabolites have been identified to date. Sixty percent is excreted in the faeces and 40% in the urine. Hepatic inducers such as rifampicin, and probably rifabutin, accelerate its metabolism and influence its plasma exposure (doxycycline AUC and half-life decreased by ~40% with rifampicin). However, whether drug efficacy is compromised remains unclear.

Clindamycin is a lincosamide antibiotic that inhibits early stages of protein synthesis at the ribosome level. It is used in malaria treatment as a valid alternative to doxycycline in pregnant women. Ninety percent is bound to plasma proteins. It is metabolized in the liver by CYP3A enzymes to several active and inactive metabolites that are excreted in the faeces. Clindamycin is a moderate inhibitor of CYP3A in vitro, and the potential for drug–drug interactions involving clindamycin is low. However, rifampicin induces CYP3A4 and could theoretically induce clindamycin metabolism and decrease its half-life. These drugs should be co-administered cautiously.

**Conclusions**

Malaria and TB are two diseases that are often found concomitantly in developing countries and can have a synergic negative effect on public health. In developed countries almost all cases of malaria are imported, but TB still has a high prevalence in some European countries, especially associated with HIV infection. Treatment of these two diseases leads to several concerns about drug–drug interactions and the potential for inducing drug resistance.

Rifampicin, a standard component of combination regimens for treating TB, has a great influence on the bioavailability and the efficacy of several drugs, not only because of the inhibition of Phase I and II enzymes of hepatic metabolism, but also because of its effect on drug absorption and distribution. It induces almost all CYP450 enzymes, it inhibits N-acetyltransferases and it alters the expression of membrane transporters. Rifampicin induces intestinal, BBB and hepatic P-glycoprotein and MRP expression, and it inhibits OATP2. Most of these inducing effects are due to PXR-increased transcription; therefore, understanding each individual’s genotype is important to explain the several unknown mechanisms behind these complex drug–drug interactions. Rifabutin is mostly used in HIV co-infected patients because it has fewer drug–drug interactions with antiretroviral agents. Although rifabutin is a weaker CYP3A4 enzyme inducer than rifampicin, it may be expected to have some effect on drug metabolism as well. In many cases, the interactions between rifampicin or rifabutin and antimalarial agents are likely but not studied and confirmed.

Moreover, the consequences of simultaneous malaria and TB treatment are not well known. In each case, the need for concomitant treatment should be carefully considered, since malaria is an acute disease and TB is a subacute disease. There are a large number of drug mechanisms that need to be explored concerning antimalarial drug activity. These may be vital to treat TB and malaria simultaneously where multidrug resistance in both diseases is common.

**Transparency declarations**

Conflicts of interest: none to declare.

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