The potential for interactions between antimalarial and antiretroviral drugs

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Introduction

The rapid increase in access to antiretroviral therapy in developing countries has brought with it new challenges. These include the unprecedented need for lifelong treatment for an infectious disease, and the pressure this will place on health services. The use of fixed dose combinations from generic manufacturers does not easily allow for individualization of dosage (e.g. with coadministered drugs for tuberculosis). Gaps in current knowledge that urgently need to be addressed are the effect of ethnicity, gender and body weight upon antiretroviral drug disposition, and defining interactions with other drugs, including antimalarial and antituberculosis drugs and traditional medicines.

Malaria is widespread across areas of the world where resources are limited, and most of these areas also bear the brunt of the HIV pandemic. There are potentially many different ways in which both diseases interact, at political, social and public health levels, as well as emerging evidence for how one disease may affect the pathogenesis and outcome of the other. At a time when access to antiretroviral drugs is increasing, and new combinations of antimalarial drugs are being evaluated, it is important that potential interactions between therapies for these two infections are also reviewed.

Pharmacology of antiretroviral drugs

That antiretroviral drugs have the ability to prolong survival and improve well-being of HIV-positive individuals is beyond question; yet their therapeutic effects may be limited by toxicity, pill burden, the need for strict adherence to treatment, emerging prevalence of resistance and the risk of developing adverse drug interactions. At least 19 drugs from three classes – nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI), are available for the oral treatment of HIV infection. Fusion inhibitors (enfuvirtide) are an additional class of parenterally administered drug.

For most countries in Africa, preferred combinations are represented by the four '3 by 5' regimens, which are made up of 2NRTI [zidovudine (ZDV) or stavudine (d4T) plus lamivudine (3TC)] plus an NNRTI [nevirapine (NVP) or efavirenz (EFV)]. Problems of cost, shelf life, storage and toxicity of PI drugs currently limits their availability and use, even with generic manufacture or discounting through United Nations drug-access initiatives. However, the emergence of NNRTI resistance will limit the useful therapeutic lifespan of NNRTI, and the use of PI in developing countries (currently available in many private clinics) is likely to grow.

The pharmacology of antiretroviral drugs will be familiar to most readers and has been detailed in previous issues of this journal [1]. A summary is provided for those unfamiliar with this topic (Table 1).

Absorption
NRTI [with the exception of didanosine (ddI)] and NNRTI are well absorbed. The absorption of PI drugs is improved with food, and this is especially important for nelfinavir where drug exposure is almost twice that

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Table 1. Pharmacokinetics of antimalarial and anti-HIV drugs.

Drug	Bioavailability (%)	Protein binding (%)	Half-life	Active metabolite	Metabolism	Excretion	Potential for interaction
Antimalarials							
Quinine	>80	70–90	8–18 h		CYP 3A4 (inhibits CYP 2D6)	Renal	
Chloroquine	100	50–70	30–60 d			Renal (mostly unchanged)	Low
Pyrimethamine	Good	94	95 h		Liver	Renal	Low
Sulfadoxine	Good	94	170 h		–	Renal/liver	Low
Proguanil	>90	75	16.5 h	Cycloguanil (half-life 20 h) (via CYP 2C19)	CYP 2C19, polymorphic	Renal	
Dapsone	>90	~50	27 h		Extensive liver metabolism; N-acetylation	Renal	
Mefloquine	75–80	>95	21.4 d		–	Liver	
Amodiaquine			5 h	Desethylamodiaquine (equipotent); (via P450)	P450	Liver	
Artemether	Good	95.4	1.4 h	Dihydroartemesenin (via CYP 3A4)	CYP 3A4; induces CYP 2C19/3A4	Liver	
Lumefantrine	Poor (<10%)	99.9	2–3 d		CYP 3A4 (inhibits CYP 2D6)	Liver	
Halofantrine	Poor	–	1–4 d	Active metabolites (desbutylhalofantrine, half-life 2–5 d); (via CYP 3A4)	CYP 3A4	Liver	Moderate; low therapeutic index
Primaquine	Well absorbed; presystemic metabolism	High	6 h		P450	Liver	Moderate; inhibits some P450 isoforms
Atovaquone	Variable	>99	2.9 d	–	–	Liver	Low
Nucleoside reverse transcriptase inhibitors							
Abacavir	83	~49	≥20 h	Prodrugs undergo three phosphorylation steps intracellularly to active drug trisphosphates		Renal (80%)	Low
Didanosine	~42	<4	~30 h		Intracellular interactions with ribavirin and with hydroxyurea	Renal (50%)	
Emtricitabine	93	<4	40 h			Renal (86%)	Low
Lamivudine	80–85	<36	17 h		Intracellular interactions in activation with zalcitabine	Renal (70%)	Low
Stavudine	~86	<4			Intracellular interactions in activation with zidovudine	Renal (40%)	Low
Zalcitabine	>80	<4		Prodrugs undergo three phosphorylation steps intracellularly to active drug trisphosphates	Intracellular interactions in activation with lamivudine	Renal (75%)	Low
Zidovudine	60–70	34–38	7 h		Intracellular interactions in activation with stavudine	Hepatic	Low
Tenofovir	25	<7	>60 h	Prodrug undergoing two phosphorylation steps to active bisphosphate	Inhibits purine nucleoside phosphorylase (interaction with didanosine)	Renal	Moderate
Non-nucleoside reverse transcriptase inhibitors							
Nevirapine	93	60	30 h		Metabolized by CYP 3A4 and CYP 2B6; inducer of CYP 3A4	Hepatic	
Efavirenz		>99	35 h		Metabolized by CYP 3A4 and CYP 2B6; inducer of CYP 3A4	Hepatic	High
Delavirdine		~98	6 h		Inhibitor of CYP 3A4	Hepatic	

Protease inhibitors	Oral bioavailability	Protein binding (%)	Plasma half-life	Active metabolite / metabolism	Route of excretion	High
Amprenavir		90	7 h	Extensive hepatic metabolism mainly via CYP 3A4; potent inhibitors of P540 CYP enzymes	Hepatic	
Atazanavir		89	8 h		Hepatic	
Indinavir	~65	60	2 h		Hepatic and renal	
Lopinavir	Poor (given with RTV)	98–99	5–6 h		Hepatic	
Nelfinavir		>98	3–5 h	M8 (via CYP 2C19; polymorphic)	Hepatic	
Ritonavir		98–99	3–5h	Used to boost other PI by enhancing bioavailability (saquinavir, lopinavir) or reducing hepatic clearance (indinavir, amprenavir, atazanavir) through inhibition of CYP 3A4 in the gut or liver	Hepatic	
Saquinavir	12	97	4 h		Hepatic	

d, days.

when taken fasting. The absorption of PI is limited by metabolic degradation by cytochrome P450 enzymes (mainly the CYP 3A4 isoform) within the gut as well as the presence of drug efflux transporters (e.g. P-glycoprotein). Ritinavir (RTV) may be used to 'boost' the bioavailability of other PI such as saquinavir (SQV) or lopinavir (LPV), mainly through inhibition of gut CYP 3A4.

Distribution

Since HIV replicates within cells, drugs that target its replication must penetrate into infected cells and anatomical compartments such as the CNS and genital tract at sufficiently high concentrations to exert their effect; failure to do so results in the establishment of a sanctuary site. The tissue and intracellular accumulation of HIV drugs is determined primarily by their physicochemical characteristics (e.g., lipophilicity, charge), by the extent of protein binding and probably by the influence of active transport (mediated by transporters such as P-glycoprotein, multidrug resistance proteins 1 and 2) [2].

Metabolism and elimination

PI drugs are extensively metabolized by cytochrome P450 enzymes, most notably the isoform CYP 3A4. In the case of nelfinavir, CYP 2C19 is also involved in the formation of the active M8 metabolite. PI have short plasma elimination half-lives (generally ≤8 h), even with RTV boosting. Excretion is mainly via the liver for all PI, with the exception of indinavir (IDV), which is also excreted by the kidney. RTV boosting reduces the hepatic clearance of IDV, amprenavir, fosamprenavir and atazanavir by inhibiting hepatic metabolism, and thereby increasing plasma concentrations of these drugs. NNRTI drugs are metabolized by CYP 3A4 and CYP 2B6. The latter may be important when considering ethnic variability in pharmacokinetics (see below). EFV and NVP have long elimination half-lives (30−35 h) than delavirdine (6 h), which is seldom used. NNRTI are excreted via the liver.

The NRTI must also undergo phosphorylation once inside cells to produce the active metabolites. There is a disparity between the plasma elimination half-lives of NRTI, which lie in the range 2−6 h, and those of the active intracellular phosphorylated metabolites, which are far longer [ZDV, 7 h; 3TC, 17 h; abacavir (ABC), 22 h; ddI, 30 h; emtricitabine, 40 h; and tenofovir, ∼60 h] and which correlate moderately or poorly with plasma concentrations of parent drug. Tenofovir, ddI, d4T and 3TC are excreted largely unchanged by the kidney; ZDV is excreted via the liver, mainly through glucoronidation.

Drug transporters in the kidney and biliary tract almost certainly play an important role in the elimination of

antiretroviral drugs but these have not yet been fully characterized.

Toxicity

The major toxicities of NRTI include rash, lactic acidosis and mitochondrial dysfunction (through inhibition of DNA polymerase γ), neuropathy (ddI, d4T, 3TC, zalcitabine), pancreatitis (ddI), anaemia/neutropenia (ZDV) and myositis (ZDV). ABC is associated with a systemic hypersensitivity reaction, which may be severe (affecting 4–8% of patients).

NVP and EFV may cause hepatotoxicity [3]. NVP may also be associated with a systemic hypersensitivity syndrome comprising fever, rash, myalgia and hepato-toxicity. NVP hypersensitivity/hepatotoxicity is associated with female gender and immune status, and women with CD4 cell count $>250 \times 10^6$ cells/l appear to be at highest risk. Preexisting liver dysfunction (such as that in chronic viral hepatitis) is also an important risk factor for drug-induced hepatotoxicity. There is some crossover in hypersensitivity between NVP and EFV. EFV is associated with CNS symptoms such as dizziness, poor sleep and bad dreams; animal reproductive toxicology studies have suggested the potential for teratogenesis. PI drugs are associated with diarrhoea and gastrointestinal disturb-ance, hepatotoxicity, nephrolithiasis (IDV), elevated lipids, glucose intolerance and body fat changes. Other recognized toxicities include osteopenia, osteoporosis and avascular necrosis.

Interindividual variability and effect of gender, weight and ethnicity

Huge (over 50-fold) variability has been observed for PI and NNRTI [4], and large variability has also been reported for intracellular active NRTI metabolites [5]. The causes of this variability are probably multifactorial and include adherence, drug interactions, body weight, gender and drug absorption. In both the Dutch [6] and UK (unpublished data) therapeutic drug monitoring schemes, women tend to have higher plasma concen-trations (and are more likely to have 'toxic' drug concentrations) of EFV and NVP than men. In addition, we have observed differences in LPV exposure according to gender and body weight [7], and one study has recently reported higher peak concentrations of IDV in Thai subjects, suggesting that individuals with very low body weight may be predisposed to IDV nephrotoxicity [8]. Ethnic differences owing to genetic variability may also play a role. Black Africans have been found to have lower EFV clearance (and consequently higher plasma con-centrations), possibly as a result of polymorphisms in drug-metabolizing enzymes such as CYP 2B6 [9,10]. One study measuring intracellular concentrations of ZDV trisphosphate observed no difference between Thai and Caucasian subjects [11]. Gender differences have been

reported in formation of the intracellular drug trispho-sphates of ZDV and 3TC [5].

Ethnic and gender differences have also been observed for drug toxicity. Lipodystrophy and ABC hypersensitivity appear to be less common in African-Americans than in Caucasians, and certain MHC haplotypes and HSP70 have been associated with ABC reactions [12]). Women have a higher risk of developing lipodystrophy and NVP hypersensitivity.

Potential for drug interactions with antiretroviral drugs

Detailed discussion of individual drug interactions involving HIV drugs is not within the scope of this article but may be found elsewhere (e.g., www.hiv-druginteractions.org). Most clinically significant drug interactions involve PI (inhibition of P450 enzymes) and to a lesser degree NNRTI (induction and/or inhibition of P450 enzymes). Since P450 enzymes (in particular CYP 3A4) are central to the metabolism of a broad array of drugs including antituberculosis drugs, anticonvulsants, antihistamines, macrolides, azole antifungal drugs, anti-arrhythmic drugs, opiates and statins, the capacity for important (and potentially dangerous) drug interactions needs to considered when prescribing these drugs. Other important interactions not involving P450 enzymes include acid-modifying drugs (such as the histamine H_2 receptor antagonists, proton pump inhibitors), which impair the absorption of IDV, atazanavir and fosampre-navir.

In contrast, NRTI have fewer interactions. Most of these are intracellular drug activations between drugs of this class or with other nucleoside analogues such as ribavirin, hydroxyurea and mycophenolic acid. One important finding is that tenofovir significantly reduces plasma concentrations of atazanavir.

Pharmacology of antimalarial drugs

Drug discovery in malaria has, by and large, been serendipitous. Mechanisms of action are still incompletely understood and have only been properly studied subsequent to long-term use [13]. A number of mechanisms are known to be involved.

- Haemoglobin digestion in the food vacuole. Chloroquine [14], amodiaquine, quinine and mefloquine all interfere with this essential process.
- The folate pathway. Sulfadoxine–pyrimethamine and the newer combination chlorproguanil–dapsone are com-petitive inhibitors of key enzymes in the folate pathway. High folate concentrations probably oppose the effects of

this drug group *in vivo* [15], whereas some additivity with trimethoprim−sulfamethoxazole may be expected.

- Alkylating agents: the artemisinin derivatives. It is thought that breakdown of a labile peroxide bridge within the sesquiterpene lactone artemisinin molecule generates free radicals that rapidly alkylate key parasite molecules [16]. Haemazoin probably catalyses the decomposition of these drugs, which may explain the large therapeutic index of the drug group. Sensitivity to the artemisinins may be declining in parts of China, but resistance *Plasmodium falciparum* is not yet a major problem. In contrast to other antimalarial drug groups, the artemisinins have marked effects on the circulating forms of the parasite, the viability of which decline soon after the start of treatment. The artemisinins have gametocytocidal effects on *P. falciparum*, and this may help to reduce transmission.
- Mitochondrial function. Atovaquone works by inhibition of cytochrome *c* reductase, which may be the basis of its synergy with the prodrug proguanil. Unfortunately, the parasite readily develops resistance to atovaquone.
- The apicoplast. The antibiotics (including tetracyclines) interfere with protein translation at this site [17].

The 4-aminoquinolines

Chloroquine is probably still the most widely used antimalarial drug in Africa. The extensive spread of resistance has severely limited its usefulness for falciparum malaria, although it remains effective for *Plasmodium ovale, Plasmodium malariae* and most cases of *Plasmodium vivax* infection.

Chloroquine is rapidly absorbed from the gut and from intramuscular or subcutaneous injections [18]. Approximately half of the absorbed chloroquine is cleared unchanged by the kidney, the rest being biotransformed in the liver to desethyl- and bisdesethylchloroquine. Although clearance is reduced in renal failure, it is not usually necessary to reduce the dose. The terminal elimination half-time is very long (1−2 months). Chloroquine is generally well tolerated but concentration-dependent adverse events are seen, including dizziness, diplopia and nausea, and, in dark skinned individuals, pruritus of the palms, soles and scalp. Rare toxic effects include photoallergic dermatitis, aggravation of psoriasis, skin pigmentation, leukopenia, bleaching of the hair and aplastic anaemia. Chloroquine can exacerbate epilepsy; when cumulative doses exceed 100 g, it may cause irreversible retinopathy.

In contrast to chloroquine, amodiaquine is extensively converted to its equipotent metabolite desethylamodiaquine, which is responsible for most of the antimalarial activity: desethylamodiaquine achieves much higher concentrations than its parent drug [19]. Another metabolite, amodiaquine-quinoneimine, has an important role in toxic reactions [20]. Amodiaquine is no longer recommended for prophylaxis because of concerns over

hepatitis and agranulocytosis, but it may be used for treatment where the risk is generally considered to be lower. Amodiaquine is increasingly used in parts of Africa at present, notwithstanding a relative lack of pharmacovigilance data.

The antifolates

The antifolates are used in fixed ratio combinations. Sulfadoxine−pyrimethamine is currently the commonest drug for uncomplicated falciparum malaria in many parts of Africa. Unfortunately resistance to this combination is causing grave concern.

Pyrimethamine is well absorbed after oral or intramuscular administration. Chlorproguanil, which can only be given orally, reaches peak plasma concentrations in 2−4 h and has a short elimination half-life: most of the antimalarial activity results from its triazine metabolite chlorcycloguanil [21]. The extent of chlorproguanil metabolism varies considerably; metabolism is catalysed by the cytochrome P450 group (mainly CYP 2C19), which is subject to genetic polymorphism. 'Poor metabolizers' of chlorproguanil sustain low or undetectable concentrations of chlorcycloguanil, but clinical trials have failed to show diminished prophylactic efficacy in such 'poor metabolizers'. Pyrimethamine and chlorproguanil are well tolerated and less prone to allergic reactions than sulphonamides or sulphones.

Of the sulphonamides and sulphones, only sulfadoxine and dapsone have been widely used in malaria chemotherapy. The elimination half-life of sulfadoxine is 100−200 h. Sulfadoxine undergoes limited phase II metabolism (to the acetylated and glucuronide derivatives). The degree of acetylation varies between populations as a result of a genetic polymorphism. Severe allergic reactions to sulphonamides are well recognized; in the case of slowly eliminated drugs like sulfadoxine, such reactions can be life threatening. Dapsone has a mean half-life of approximately 26 h and is associated with a range of concentration-related and idiosyncratic adverse reactions. However, a recent large clinical trial of chlorproguanil−dapsone reported the combination to be safe and well tolerated [22].

The artemisinin-derivatives

Artemether, artesunate and dihdroartemisinin are in common clinical use. They may be used parenterally for severe malaria syndromes. For uncomplicated malaria, they are usually employed in combination with other drugs because this shortens the length of treatment. Many public health strategies worldwide are now dependent upon this drug class, with lumefantrine−artemether (Coartem) as the only fixed-ratio 'artemisinin combination therapy' widely available. Artemisinin and its

derivatives (such as artesunate and artemether) are rapidly hydrolysed *in vivo* to a biologically active metabolite, dihydroartemisinin. Both parent drugs and dihydroartemisinin are eliminated rapidly [23]. The role of other metabolites in humans requires further study. The hydrolysis of artesunate is so rapid that it may be considered a prodrug for dihydroartemisinin. Dihydroartemisinin is also in use as a drug and is being developed in fixed-ratio combination with piperaquine.

Artemesinins are safe and well tolerated. The main current concern centres on reproductive safety [24,25], with embryotoxic effects reported from China and morphological abnormalities (mostly shortening of long bones) seen in some animal studies. It is, therefore, reassuring that the extensive use of artemisinins in large numbers of individuals from China and Southeast Asia has been safe, and published data on nearly 1000 pregnancies (about 100 from the first trimester) have shown no evidence of treatment-related adverse pregnancy outcomes [26]. Pharmacovigilance systems are now being established. The World Health Organization has concluded that the artemisinins (1) cannot be recommended for treatment of malaria in the first trimester (but should not be withheld if they are life saving for the mother) and (2) should only be used in later pregnancy when other treatments are considered unsuitable. It should be remembered that malaria in pregnancy can be extremely dangerous, and that no antimalarial drug is free from concerns over reproductive safety.

The quinolinemethanols

Quinine is less potent than chloroquine and has a narrow therapeutic range but resistance is rare in Africa. Parenteral quinine is the drug of first choice for severe malaria, and oral quinine is an option for uncomplicated malaria where multidrug resistance is a problem. Quinine is extensively bound to plasma proteins, principally to the acute-phase reactant α_1-acid-glycoprotein. In healthy subjects, approximately 80% of the total plasma quinine concentration is bound, but in patients with malaria, α_1-acid-glycoprotein concentrations rise, and approximately 90% is bound; this may explain the apparently lower toxicity of high quinine concentrations in patients with malaria compared with that in patients who have taken a deliberate overdose. Quinine undergoes extensive hepatic biotransformation and less than 20% of the drug is excreted unchanged in urine. The elimination half-time of quinine is shorter in health (11 h), longer in adults with uncomplicated malaria (16 h) and greater still in adults with cerebral malaria (18 h). 'Cinchonism' (tinnitus, deafness, headache, nausea and visual disturbance) is common at therapeutic levels of quinine and does not warrant dose reduction. Rare, but potentially life-threatening, adverse events are hypersensitivity reactions (rashes, thrombocytopenia, leukopenia, dissem-

inated intravascular coagulation, haemolytic–uraemic syndrome), hypoglycaemia, visual impairment, serious cardiovascular compromise, coma and seizures.

Mefloquine, which has structural similarities with quinine, is widely used in Southeast Asia, usually combined with an artemisinin. Cost limits its use in Africa. This drug is very slowly eliminated: the half-life ranges from 15 to 33 days and steady state (in the setting of prophylaxis) is reached after 8 weeks. Dose-related symptomatic adverse reactions are common, usually mild and most frequently gastrointestinal [27]. 'Serious' CNS events, including seizures, are estimated to occur in about 1 in 10 000 prophylactic users, which is about the same reported rate as chloroquine. The estimated frequency of non-serious CNS events (including headache, dizziness, insomnia and depression) varies between 1.8 and 7.6% (and is generally higher in females than males); these proportions are similar to those for chloroquine, but approximately fivefold higher than reported by patients taking no prophylaxis. Mefloquine use during pregnancy increases the risk of stillbirth, and pregnancy should be excluded before use.

Halofantrine and lumefantrine

Halofantrine is seldom used because of toxicity, but lumefantrine [28] is used, only in combination with artemether (Coartem), for the treatment of uncomplicated multiresistant falciparum malaria. Lumefantrine is incompletely bioavailable from the gut and this may vary markedly during acute malaria. Bioavailability is increased by coadministration with food. It is eliminated with a half-life of approximately 1–6 days. Lumefantrine is well tolerated and, unlike halofantrine, does not seem to prolong the QT interval [29]. There are concerns that Coartem may affect audiometric tests, but the relevance of this to clinical practice remains to be established.

Other antimalarial drugs

Atovaquone–proguanil is used for treatment and prophylaxis of multiresistant falciparum malaria. Given its expense, it has little relevance to public health in most tropical countries. Primaquine is an 8-aminoquinoline primarily used for preventing recurrence of benign malaria by targeting exoerythrocytic stages of *P. vivax* and *P. ovale* in the liver. Major side effects are methaemoglobinaemia and haemolysis (in patients with deficiency of glucose 6-phosphate dehydrogenase). Certain antibiotics, particularly clindamycin and the tetracyclines, have useful antimalarial activity. They are never used alone but are most frequently added to quinine for patients who can take oral medication; this practice is most commonly needed in areas of intense drug resistance (such as Southeast Asia) where clearance of parasitaemia with quinine may be prolonged.

Table 2. Anticipated drug interactions between antimalarial and antiretroviral drugs.

	Quinine	CLQ	SP	Pro	Dap	MFQ	ADQ	Art	LUM	HF	ATQ	PQ
Protease inhibitors												
Saquinavir	▽[1]	√	√	√[2]	√[3]	√[4]	ND	ND[6]	●[7]	●[7]	√	ND
Ritonavir	▽[1]	▽	▽	▽[2]	√[3]	√[4]	ND	ND[6]	●[7]	●[7]	▽[8]	ND
Indinavir	▽[1]	√	√	√[2]	√[3]	√[5]	ND	ND[6]	●[7]	●[7]	√[8]	ND
Nelfinavir	▽[1]	√	√	√[2]	√[3]	√[5]	ND	ND[6]	●[7]	●[7]	√	ND
Amprenavir	▽[1]	√	√	√[2]	√[3]	√	ND	ND[6]	●[7]	●[7]	√[9]	ND
Lopinavir	▽[1]	√	√	√[2]	√[3]	√	ND	ND[6]	●[7]	●[7]	▽[9]	ND
Atazanavir	▽[1]	√	●	√[2]	√[3]	√	ND	ND[6]	●[7]	●[7]	√	ND
NNRTI												
Nevirapine	▽[1]	√	√	√	√	√	ND	ND[6]	▽[7]	▽[7]	√	ND
Efavirenz	▽[1]	√	√	√	√	√	ND	ND[6]	▽[7]	▽[7]	√	ND
Delavirdine	▽[1]	√	√	√	√	√	ND	ND[6]	●[7]	●[7]	√	ND
NRTI												
Zidovudine	√	√	√	√	√	√	√	√	√	√	√[10]	√
Lamivudine	√	√	√	√	√	√	√	√	√	√	√	√
Didanosine	√	√	√	√	√[11]	√	√	√	√	√	√	√
Stavudine	√	√	√	√	√	√	√	√	√	√	√	√
Abacavir	√	√	√	√	√	√	√	√	√	√	√	√
Zalcitabine	√	√	√	√	√	√	√	√	√	√	√	√
Emtricitabine	√	√	√	√	√	√	√	√	√	√	√	√
Tenofovir	√	√	√	√	√	√	√	√	√	√	√	√
Fusion inhibitors												
Enfuvirtide	√	√	√	√	√	√	√	√	√	√	√	√

Interactions are assessed as: ND, no clear data, actual or theoretical, to indicate whether an interaction will occur; √, no clinically significant interaction, or interaction unlikely based on knowledge of drug metabolism; ▽, potential interaction that may require close monitoring, alteration of drug dosage or timing of administration; ●, interaction likely, do not use or use with caution.
NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; CLQ, chloroquine; SP, sulfadoxine–pyrimethamine; Pro, proguanil; Dap, dapsone; MFQ, mefloquine; ADQ, amodiaquine; Art, artenusate; LUM, lumefantrine; HF, halofantrine; ATQ, atovaquone; PQ, promaquine. Evaluation of interactions between antiretroviral and antimalarial drugs here refer to specific points in a numbered list above. Adapted with permission from www.hiv-drug-interactions.org. As new data emerges, updates to this table will be posted on this website.

Pharmacokinetic interactions between antiretroviral and antimalarial drugs

In general, pharmacokinetic interactions involve mostly HIV PI and NNRTI classes. PI (especially RTV) are amongst the most potent inhibitors of cytochrome P450 enzymes (CYP 3A4, CYP 2B6, CYP 2D6 and others) licensed for use in humans, and their role in pharmacokinetic interactions is made more complex since some PI also induce their own metabolism (e.g. RTV, nelfinavir) and can induce other enzymes responsible for drug metabolism. PI may also inhibit the multidrug efflux transporter P-glycoprotein. These properties are utilized when RTV is added to other PI to enhance bioavailability (SQV, LPV) or to reduce hepatic clearance (IDV, amprenavir, atazanavir) through inhibition of CYP 3A4 in the gut or liver, respectively. The NNRTI drugs NVP and EFV are inducers of CYP 3A4, while delavirdine is an inhibitor of CYP 3A4 (and has also been used to boost PI).

However, these properties contribute to the high risk of drug interactions (some of which are potentially serious) through the inhibition or induction of metabolism of a broad array of drugs which undergo hepatic detoxification or bioactivation. Data from clinical studies evaluating interactions between antiretroviral and antimalarial drugs are sparse, and much of the risk assessment for drug interactions derives from knowledge of the pharmacokinetics of these drugs, or more rarely from *in vitro* preclinical screening. In the absence of definitive data, a risk assessment of potential drug interactions involving antiretroviral and antimalarial drugs is presented in Table 2.

The following points are noteworthy and are referred to by number in Table 2.

1. Quinine is extensively metabolized by CYP 3A4. Exposure could be increased by RTV or RTV-containing boosted PI regimens, and by delavirdine. Induction of CYP 3A4 by NVP and EFV could reduce plasma quinine exposure.
2. Since proguanil is a prodrug and is partially activated (CYP 2C19) to cycloguanil, there is concern that inhibition of metabolism by RTV or RTV-containing boosted PI regimens will reduce pharmacological effect. However, synergy with atovaquone is related to proguanil, not cycloguanil. When the drugs are coadministered, CYP 2C19 inhibition could potentially enhance this synergistic effect, which may offset decreased cycloguanil formation.

3. Metabolism of dapsone is mainly by N-acetylation with a component of N-hydroxylation via multiple CYP P450 enzymes. Clinically, significant interactions are unlikely but cannot be excluded.

4. Mefloquine had variable effect on RTV metabolism: no interaction was noted after a single dose but ritonavir plasma area under the concentration–time curve (AUC) was reduced by 31% and maximal plasma concentrations (C_{max}) by 36% after multiple dosing. Pharmacokinetics of mefloquine were not significantly influenced by RTV [30].

5. A case report has observed no drug interaction between IDV or nelfinavir and mefloquine [31].

6. Artemether is metabolized via CYP 3A4 to dihydroartemesinin (although both compounds have antimalarial activity, dihydroartemesinin has greater potency). Inhibition of CYP 3A4 would reduce dihydroartemesinin but increase artemether and potentially increase the short half-life of artemether (1–2 h). The effects of PI and NNRTI are unclear.

7. Lumefantrine and halofantrine are extensively metabolized by CYP 3A4. Inhibition of halofantrine metabolism could potentially prolong QT interval; given the narrow therapeutic index of this drug, combination with PI is contraindicated and NVP and EFV should be used with caution. Lumefantrine does not seem to prolong the QT interval and is much safer than halofantrine. Nevertheless, interactions with PI and NNRTI drugs are likely, and the manufacturer's *Summary of Product Characteristics* advises that coadministration of CYP 3A4 inhibitors such as PI are contraindicated. Given the increasing use of lumefantrine–artemether for malaria, we recommend caution when using PI/NNRTI. The need for interaction data is urgent and studies should be prioritized to address this gap in knowledge.

8. Atovaquone lowers IDV exposure, reducing trough plasma concentrations by ∼23% [32]. A healthy volunteer study observed an AUC decrease of 5% for IDV but an increase in atovaquone AUC of 13% and C_{max} of 16% when the drugs were coadministered [33]. No dosage adjustments are necessary for atovaquone when given with IDV. The clinical significance of lowered IDV concentrations is uncertain since these were healthy volunteer studies carried out without RTV boosting (which is no longer the preferred means of giving IDV). Moreover, clinical studies have shown higher plasma IDV in Thai patients (who have lower body weight) and, given the toxicity of IDV at higher doses, dosage adjustments are not indicated for IDV (boosted with RTV) when dosed with atovaquone or malarone.

9. LPV may decrease plasma concentrations of atovaquone. The clinical significance of this is not known; however, increases in atovaquone dosage may be needed. [34].

10. Atovaquone decreases the oral clearance of ZDV, leading to a 35 ± 23% increase in its plasma AUC. The clinical significance of this is not known, and no dose modification is recommended.

11. Previous formulations of ddI (buffered tablets) decreased dapsone concentrations, in some cases leading to failure of prophylaxis for *Pneumocystis carinii* pneumonia [35]. No interaction has been observed with newer formulations.

Pharmacodynamic interactions between antiretroviral and antimalarial drugs

Disease interactions between malaria and HIV infection

Disease interactions between malaria and HIV infection have been discussed in detail elsewhere. Studies from Africa have reported an increase in the prevalence of *P. falciparum* in adults with HIV infection [36,37]. HIV-infected pregnant women with falciparum malaria have greater parasite density in peripheral blood and placenta, and are at greater risk of fever, severe anaemia and adverse birth outcomes than HIV-uninfected women. This risk (which is typically highest in primigravidae without HIV infection) is maintained throughout subsequent pregnancies in HIV-positive women [38]. HIV infection was also associated with severe/complicated malaria and death from falciparum malaria in Hlabisa district, an area of unstable malaria transmission in KwaZulu Natal [39]. Symptomatic malaria appears to increase HIV viral load, although the clinical implications of this are uncertain [40].

Antiviral properties of antimalarial drugs

Chloroquine suppresses HIV-1 and HIV-2 replication *in vitro* (as does its analogue hydroxychloroquine) [41,42] possibly by inhibition of HIV gp120. *In vitro* studies examining chloroquine in HIV-infected cells has shown some additivity with ZDV and synergy with some PI drugs in T cell lines [42,43]. However, only modest anti-HIV activity has been observed for chloroquine and mefloquine and no antiviral activity for halofantrine, amadiaquine and mepacrine [44]; significant synergy was observed between mefloquine and the PI SQV, and antagonism between chloroquine and SQV. The clinical significance of these findings is uncertain. What remains clear is that the antiretroviral effects of chloroquine are modest when compared with that of combination antiretroviral therapy. Moreover, one pilot randomized placebo-controlled study (CHARGE) from Rwanda demonstrated no effect of chloroquine on HIV load in breast milk of HIV-positive mothers [45].

Examination of the *Plasmodium* genome reveals the presence of several aspartate and cysteine proteases that have key roles, such as digestion of haem within the food vacuole. Specific antimalarial PI drugs are being developed as new therapy for this disease, but knowledge of their site of action would suggest potential negative

interaction with 4-aminoquinolines such as chloroquine. Whether or not HIV PI drugs exhibit any antimalarial properties *in vitro* or *in vivo* is unclear. Antimalarial effects with SQV and RTV at pharmacologically achievable concentrations have been observed *in vitro* [46], although the high protein binding of these drugs *in vivo* and lack of data on their penetration into red blood cells suggests that further work is required to establish the clinical relevance of these findings.

The HIV PI drugs RTV and SQV have been shown *in vitro* to downregulate expression of CD36 [47], a key receptor mediating the cytoadhesion of parasitized erythrocytes to endothelial cells. This raises the possibility that HIV PI may alter disease outcomes of coinfected patients. Whether or not this finding is of importance *in vivo* is not known.

Trimethoprim–sulfamethoxazole and malaria

Three randomized trials (involving 1416 individuals) in Africa have demonstrated a beneficial effect of prophylactic daily (960 or 480 mg) trimethoprim–sulfamethoxazole (cotrimoxazole) in preventing death and illness in adults with early and late HIV disease (reviewed by Grimwade and Swingler [48]). Another similar study in 541 HIV-infected children in Zambia was recently prematurely terminated when significantly lower mortality was demonstrated in the trimethoprim–sulfamethoxazole arm. The increasingly widespread use of this combination may have implications for malaria as it has modest anti-*Plasmodium* activity and could treat malaria infections. Alternatively (and particularly in areas of the world where resistance to sulfadoxine–pyrimethamine is prevalent), trimethoprim–sulfamethoxazole could select for mutations in the genes for dihydropteroate synthetase and dihydrofolate reductase, driving up rates of resistance to sulfadoxine and pyrimethamine, respectively. However, the selection of these resistance mutations is weak with trimethoprim–sulfamethoxazole compared with that with sulfadoxine–pyrimethamine. Much will rest on prevailing community rates of resistance and the doses/regimens of trimethoprim–sulfamethoxazole used. For example, lower doses or three times weekly regimens (note: all African trials used daily trimethoprim–sulfamethoxazole) or poor adherence to trimethoprim–sulfamethoxazole could select for resistant falciparum infection, and the window for selection of resistance may be larger where a degree of parasite resistance already exists. Methodological difficulties still exist for determining resistance to antifolate drugs. However, programmes such as EANMAT have attempted, to a degree, to standardize *in vivo* test conditions across several countries. It is vitally important for systems to be put in place to allow serial surveillance for drug resistance (phenotype and genotype) in communities where trimethoprim–sulfamethoxazole treatment programmes are implemented.

Overlapping syndromes and toxicity

Overlapping syndromes or toxicity profiles may complicate the clinical picture in malaria and HIV coinfection and render it difficult to isolate the causative factor. Typical examples include:

- *fever*: malaria, opportunistic infections, HIV itself, drug hypersensitivity such as that encountered with ABC or NVP
- *anaemia*: common finding in HIV-infected patients in Africa; may be HIV related or caused by drugs (ZDV, dapsone, trimethoprim–sulfamethoxazole), haemolysis (e.g. in patients with deficiency of glucose 6-phosphate dehydrogenase or malaria infection)
- *agranulocytosis or pancytopenia*: can be caused by amadiaquine, dapsone, trimethoprim–sulfamethoxazole, ZDV or by infection including with HIV
- *rash*: most antimalarial and anti-HIV drugs can cause rash
- *Stevens–Johnson syndrome/toxic epidermal necrolysis*: NVP, ABC and, rarely, sulfadoxine–pyrimethamine (1:20 000)
- *lactic acidosis*: NRTI, malaria
- *hepatitis*: amadiaquine, NNRTI, PI, NRTI, background chronic hepatitis B infection
- *renal failure*: malaria nephritis, HIV nephropathy, microsporidiosis, sulphonamides (at dosage used for *P. carinii* pneumonia treatment), IDV, tenofovir.

Conclusions

Despite the wide prevalence of malaria and HIV in many parts of the tropics, knowledge of how these two important diseases interact is still hampered by lack of knowledge in many key areas. Some interactions between treatments for these two diseases may occur, but these are anticipated to be mostly minor, except for lumefantrine and halofantrine with PI or NNRTI. The interaction between quinine and PI/NNRTI needs to be evaluated. However, drug interactions form only a very small part of the potentially massive number of ways in which HIV and malaria interact to the detriment of human health.

Note: This was part of a presentation to a WHO Technical Consultation on Interactions between HIV and Malaria, Geneva June 2004.

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