Interactions between Antimalarial Agents and Antiretrovirals

Note: *The intention of this chart is to summarize the literature on drug interactions between antimalarial and antiretroviral agents. Suggestions on the management of these interactions are provided when possible. However, clinical judgment in the context of the patient is advised.*
Delavirdine drug interactions are not included in this table

Overview of Antimalarial Agents

Generic Name	Trade Name(s)	Pharmacologic Class
Amodiaquine	Camoquin, Flavoquine	Quinine Derivative
Artemether		Artemisinins
Artemether/ Lumefantrine	Coartem/Riamet	Combination Antimalarials
Artemisinin		Artemisinins
Artesunate	Arzuna	Artemisinins
Atovaquone/ Proguanil	Malarone	Combination Antimalarials
Chloroquine	Aralen	Quinine Derivative
Clindamycin	Dalacin C	Antibiotics
Dapsone/ Pyrimethamine	Maloprim or Deltaprim	Combination Antimalarials
Dihydroartemisinin		Artemisinins
Doxycycline	Vibramycin	Antibiotics
Halofantrine	Halofan	Halofantrine
Mefloquine	Lariam	Quinine Derivative
Primaquine	Primaquine	8-Aminoquinolines
Pyrimethamine/ Sulfadoxine	Fansidar	Combination Antimalarials
Quinidine	Qualaquin, Quindex, others	Quinine Derivative
Quinine	Pro-Quinine, Quinine-Odan, Teva-Quinine	Quinine Derivative
Tetracycline	Achromycin	Antibiotics
Trimethoprim/ Sulfamethoxazole	Co-trimoxazole, Septra, Septrin	Combination Antimalarials

Antimalarial Agent (Brand)	Pharmacokinetic Characteristics	Relevant HIV Drug Interactions *Suggested Management
Quinine Derivatives		
Amodiaquine (Camoquin, Flavoquine)	Metabolism: via CYP 2C8 to N-desethylamodiaquine (DEAQ), with amodiaquine being up to threefold more potent than DEAQ[1] However, as metabolism to DEAQ occurs rapidly, it is considered the major active component.	NRTI · **Zidovudine**: overlapping adverse effect profile (agranulocytosis, pancytopenia, hepatitis).[2] In one study of amodiaquine + artesunate for treatment of malaria in HIV-infected children, risk of neutropenia was significantly higher in those on ART (75 vs. 26%, p=0.001).[3] 11/12 had AZT in their regimen. All HIV+ children were also on cotrimoxazole prophylaxis. *Monitor CBC + ALT if coadministering. NNRTI · **Efavirenz**: Inhibits CYP 2C8 in vitro and therefore may ↑ amodiaquine levels.[4] This should not affect therapeutic efficacy as both amodiaquine and its metabolite DEAQ are active antimalarials, but it may have implications for toxicity. In a case report 114% and 302% ↑ AUC of amodiaquine when administered with EFV and artesunate in two HIV patients.[5] Both patients developed asymptomatic but significant elevations in hepatic transaminases 5-6 weeks following treatment and the study was terminated (ALT peaks 206, 868 U/L, AST 78, 559 U/L). *Study authors suggest liver function monitoring may be appropriate in individuals requiring amodiaquine/artesunate therapy for malaria in the setting of chronic EFV therapy. • **Nevirapine**: In an open-label, parallel group study, the kinetics of amodiaquine-artesunate (AQ-AS) 600/200 mg QD for 3 days were compared in HIV-positive subjects on stable nevirapine-based therapy vs. ART-naïve controls. No significant differences in AQ or DEAQ kinetics were noted between the groups.[6] PIs · **SQV, LPV, TPV,[4] high-dose RTV[7]** were potent CYP 2C8 inhibitors in vitro at clinically relevant concentrations which may increase the risk of amodiaquine adverse effects if coadministered.

Chloroquine (Aralen)	Metabolism: 50% excreted renally unchanged; CYP 3A4 and 2D6 metabolize to active metabolites mono- and bis-desethyl chloroquine.[8] Enzyme Inhibition: some CYP 2D6; however, effect less pronounced in vivo[9]	PIs · **Saquinavir**: one in vitro study suggested antagonistic HIV effects between chloroquine and SQV,[10] however, another found a synergistic anti-HIV effect between the two drugs.[11] Clinically significant effects unlikely.[12] · **Ritonavir**: potential for increase in chloroquine levels due to inhibition of CYP 3A4 and 2D6. This interaction has not been studied.[12] Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in chloroquine levels due to inhibition of CYP 3A4 and 2D6. This interaction has not been studied. Other · **Co-trimoxazole**: potential increased risk of cardiotoxicity (QT-interval prolongation) when used concurrently.[13, 14] Theoretical interaction, unlikely to be clinically significant.
Mefloquine (Lariam)	Metabolism: via CYP 3A4 to inactive carboxy metabolite[9, 12]	***Avoid use in treatment in pregnancy[15] and in prophylaxis in 1st trimester of pregnancy** (↑ risk of spontaneous abortion[16]) unless perceived benefits outweigh the risks. If a woman who is receiving mefloquine prophylaxis becomes pregnant, this is not an indication for termination of pregnancy. Drug of choice in 2nd and 3rd trimester in chloroquine-resistant areas for chemoprophylaxis in pregnant women travelers.[17, 18] NNRTIs Potential for ↓ mefloquine levels due to CYP 3A induction PIs · **Ritonavir**: 31% ↓ in AUC and 43% ↓ in Cmin of ritonavir after multiple concurrent dosing; mefloquine pharmacokinetics unchanged[19]. *Likely safe to co-administer without dose adjustments.[12] · **Nelfinavir and indinavir**: Report of two patients on stable HAART regimens, one on nelfinavir 1250mg bid and one on indinavir 800mg tid, both taking mefloquine 250mg weekly for at least 16 weeks for malaria prophylaxis.[20] Levels of the PIs and mefloquine were therapeutic and no side effects were reported. · **Tipranavir (unboosted)**: Potential for ↓ mefloquine levels due to CYP3A induction Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in mefloquine

		levels due to inhibition of CYP 3A4. This interaction has not been studied. Other · **Rifampin**: 68% ↓ AUC and 19% ↓ Cmax of mefloquine likely due to induction of CYP 3A4 by rifampin and therefore increased risk of protozoal resistance and treatment failure.[21] *Study authors recommend avoiding simultaneous use of rifampin and mefloquine.

Quinine	Metabolism: via CYP 3A4 (minor contribution from 2C19) to active metabolite 3-hydroxyquinine (toxic); also 20% excreted renally unchanged[9]	NNRTIs · **Efavirenz and etravirine** may ↓ quinine exposure to subtherapeutic range due to induction of CYP 3A4.[9, 22] *Monitor for reduced clinical effectiveness (response of parasitemia) and quinine levels if possible; dose-adjust as necessary. · **Nevirapine:** A single 600mg dose of quinine was administered to 14 patients on and off steady-state nevirapine 200mg bid.[23] Compared to quinine alone, quinine + nevirapine resulted in ~AUC ↓33%, Cmax ↓36%, $t_{1/2}$ ↓25% and oral clearance ↑33% of quinine. Cmax and AUC of the metabolite 3-hydroxyquinine and ratio AUC metabolite:quinine also increased significantly in the presence of nevirapine. Authors suggest an ↑ in quinine dose may be required when given with nevirapine. *Monitor for reduced clinical effectiveness (response of parasitemia) and quinine levels if possible; dose-adjust as necessary. Case report of an HIV-positive patient on abacavir, lamivudine and nevirapine who developed Plasmodium falciparum malaria and failed to respond to therapy with quinine, amoxicillin/clavulanic acid and clarithromycin. A negative interaction between nevirapine and quinine was suspected, and the patient was switched to atovoquone/ proguanil(Malarone®) with improvement and subsequent discharge after 48 hours.[24] PIs · **All protease inhibitors**: potential for ↑ quinine levels through inhibition of CYP 3A4-mediated quinine metabolism. *Caution warranted; monitor closely for adverse effects, including cardiac monitoring or ECG monitoring of QT interval with IV quinine.[12, 25] Consider therapeutic drug monitoring of quinine if possible with maintenance dose-adjustment as necessary. · **Lopinavir/ritonavir:** In healthy volunteers, steady-state lopinavir/ritonavir significantly decreased the exposure of quinine and its major active metabolite, 3-hydroxyquinine, in both total and free (unbound) forms. A decline in quinine exposure may compromise clinical efficacy.[26] · **Ritonavir:** Ten healthy volunteers on steady-state ritonavir 200mg bid received a single dose of quinine 600 mg.[27] Both

		the AUC and Cmax of quinine increased about 4-fold in the presence of ritonavir, and quinine $t_{1/2}$ increased from 11.15 to 13.37 hrs. The metabolism of quinine to its major metabolite, 3-hydroxyquinine, was markedly inhibited by ritonavir. Ritonavir pharmacokinetics were not affected. Quinine dose adjustment necessary when administered with ritonavir. · **Tipranavir** (unboosted) may ↓ quinine exposure to subtherapeutic range due to induction of CYP 3A4. Monitor for reduced clinical effectiveness (response of parasitemia) and quinine levels if possible; dose-adjust as necessary. <u>Integrase inhibitor</u> • **Elvitegravir/cobicistat**: potential for increase in quinine levels due to inhibition of CYP 3A4. This interaction has not been studied. <u>Other</u> · **Rifampin**: ↓ quinine levels due to increased clearance from rifampin-mediated induction of CYP 3A4. ***Avoid combination if possible** due to significantly higher malaria treatment failure rates when used in combination (5-fold increase in likelihood of malaria recrudescence compared to quinine alone).[28] Quinine dose should probably be increased in patients already receiving rifampin for treatment of TB.[23]
Quinidine (Qualaquin, Quindex, others)	<u>Metabolism</u>: via CYP 3A4 <u>Enzyme Inhibition:</u> Potent inhibitor of CYP 2D6[9]	<u>NNRTIs</u> · **Nevirapine, efavirenz, etravirine**: potential for ↓ quinidine concentration and therapeutic failure. *Caution warranted**;** therapeutic drug monitoring recommended if available.[12, 21] <u>PIs</u> · **All protease inhibitors**: ↑ quinidine exposure due to inhibition of CYP 3A4 increases the likelihood of cardiotoxic adverse effects from quinidine. ***Combination not recommended**. If necessary to use concurrently, monitor closely for adverse effects, including cardiac monitoring, consider therapeutic drug monitoring of quinidine with dose-adjustment as necessary. → **Contraindicated by manufacturer**: in combination with **NFV, RTV, SQV, tipranavir/RTV**[29-32] → Combination cautioned by manufacturer: ATV, darunavir, IDV, LPV/RTV[33-36] · **Tipranavir** alone (unboosted) may ↓ quinidine exposure to subtherapeutic range due to induction of CYP 3A4. Monitor

		for reduced clinical effectiveness (response of parasitemia) and quinine levels if possible; dose-adjust as necessary. Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in quinidine levels due to inhibition of CYP 3A4. This interaction has not been studied. Other · **Rifampin**: ↓ quinidine plasma levels and effectiveness via induction of CYP 3A4[37, 38]. *Consider quinidine dose increase if using concurrently – monitor quinidine plasma levels if possible.[12]
Artemisinins		
Artemisinin	Metabolism: primarily via CYP 2B6, with CYP 3A4 likely playing a role in patients with decreased CYP 2B6 activity, to inactive metabolites[9, 39] Enzyme Induction: may induce CYP 2C19[9]	***Not recommended for 1st trimester of pregnancy** but should not be withheld if lifesaving for the mother; may used in later pregnancy when other treatments are considered unsuitable.[40] Some reports of potential embryotoxicity and morphological abnormalities in animal studies,[41] however, in almost 1000 documented cases of exposures during pregnancy, no adverse pregnancy effects on the mother or fetus have been reported.[42] NNRTIs: potential ↓ in artemisinin levels due to CYP 2B6 induction PIs: potential ↓ in artemisinin levels due to induction of CYP 2B6 by **ritonavir;** In vitro study suggesting potential antagonism of artemisinin endoperoxide activity vs. *P. falciparum* when combined with PIs (studied PIs included RTV, SQV, IDV). Clinical significance is unknown, however caution is warranted with artemisinin monotherapy and PIs.[43] · **Ritonavir:** Thirty-four healthy subjects were randomized to receive pyronaridine/artesunate (PA) alone for 3 days or with steady-state ritonavir 100 mg BID. In the presence of ritonavir, artesunate AUC ↑ 27% and DHA AUC ↓ 38%, while pyronaridine pharmacokinetics were not affected. Ritonavir exposure was increased 3.2-fold in the presence of PA.[44] Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in artemisinin levels due to inhibition of CYP 3A4. This interaction has not been studied.
Dihydroartemisinin	Metabolism: unclear, likely metabolized in the liver by glucuronidation and eliminated via biliary and renal excretion[9]	***Pregnancy** see artemisinin entry **Nelfinavir, ritonavir, tipranavir:** Caution may be warranted when using with dihydroartemisinin as these PIs may induce

		glucuronyltransferase activity.
Artemether	Metabolism: via CYP 3A4/5 to active metabolite dihydroartemisinin (more potent antimalarial than parent compound)[9] Enzyme Induction: CYP 3A4 and CYP 2C19[9] Enzyme Inhibition: potential CYP 1A2 inhibition[45]	*__Pregnancy__ see artemisinin entry All PIs (**see artemether/lumefantrine and artemisinin entries**) · potential ↓ in artemether's conversion to active metabolite via CYP 3A4 inhibition. *Likely not clinically significant, as parent also active, but data lacking.[12] NNRTIs (**see artemether/lumefantrine entry**) · potential ↓[11] or ↑ in artemether's conversion to active metabolite via CYP 3A4 inhibition or induction (clinically, induction generally predominates). *Likely not clinically significant, but data lacking.[12] Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in artemether levels due to inhibition of CYP 3A4, and possible ↓ elvitegravir and cobicistat concentrations. This interaction has not been studied; avoid combination if possible.
Artesunate (Arzuna)	Metabolism: rapidly metabolized to dihydroartemisinin (active form) in vivo, then glucuronidated.[9]	*__Pregnancy__ see artemisinin entry
8-Aminoquinolines		
Primaquine	Metabolism: via CYP 1A2, 2D6, 3A4[46], to inactive carboxyprimaquine. Non-CYP-mediated oxidative processes may also play an important role in metabolism.[9]	***Avoid in pregnancy due to ↑ risk of hemolysis and methemoglobinemia in the fetus; use chloroquine prophylaxis for the duration of the pregnancy, then use primaquine after delivery**.[16] NRTIs · **Zidovudine**: both drugs may cause hematotoxicity[12, 47] therefore, the potential exists for additive hematotoxicity when used in combination. *Screening for glucose-6- phosphate-dehydrogenase deficiency prior to use should eliminate the risk of serious hematological toxicity from primaquine. NNRTIs/PIs As multiple metabolic pathways are involved in primaquine metabolism, drug interactions are difficult to predict. No published reports of interactions with NNRTIs/PIs. Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in primaquine levels due to inhibition of CYP 3A4 and 2D6. This interaction has not been studied.
Halofantrine		

Halofantrine (Halofan)	Metabolism: via CYP 3A4 to active metabolite N-desbutylhalofantrin (parent compound has a narrow therapeutic window and is cardiotoxic)[9]	Contraindicated in pregnancy[48] Food - Ingestion with food, especially when high in fat, markedly increases serum levels NNRTIs · **Efavirenz, etravirine, nevirapine:** halofantrine has a narrow therapeutic index and potential inhibition[11] or induction of CYP 3A4 by NNRTIs may ↑ toxicity or ↓efficacy of halofantrine. Clinically, induction of CYP 3A4 generally prevails with NNRTIs. Avoid combination if possible, use with caution if necessary. PIs · **All (APV, ATZ, Darunavir, IDV, LPV, NFV, RTV, SQV, Tipranavir/RTV)**: ↑ halofantrine plasma levels ↑ risk of halofantrine-induced cardiotoxicity due to inhibition of CYP 3A4 by PIs.[12] **Avoid combination.** Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in halofantrine levels due to inhibition of CYP 3A4. This interaction has not been studied.
Antibiotics		
Clindamycin (Dalacin C)	Metabolism: via CYP 3A4[49]	None known Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in clindamycin levels due to inhibition of CYP 3A4. This interaction has not been studied.

Doxycycline (Vibramycin)	Metabolism: Not fully elucidated. May be metabolized in the liver, excreted unchanged in urine and bile or partially deactivated in the intestine by chelate formation[12, 50]	**Contraindicated in pregnancy** NNRTIs, PIs: • The effect of doxycycline on antiretroviral drug levels was assessed in an open-label study of HIV-positive subjects on standard dose cART (n=1 ATV, n=14 ATV/r, n=23 LPV/r, n=17 EFV, n=10 NVP) who started doxycycline for malaria prophylaxis. ARV Ctrough were measured after at least 15 days of doxycycline therapy. No statistically significant effect on PI or NNRTI concentrations was noted, and no patient was infected with malaria.[51] Other · **Rifampin**: 130% ↑in doxycycline clearance when used in combination with rifampin and significantly lower doxycycline AUC have been reported; possibly due to induction of CYP enzymes involved in doxycycline metabolism.[52] *Avoid combination for malaria prophylaxis if possible. Monitor closely for therapeutic efficacy of doxycycline if using in combination.
Tetracycline (Achromycin)	Metabolism: none; excreted unchanged in urine and bile[12]	**Contraindicated in pregnancy** No known drug interactions with antiretrovirals
Combination Antimalarials		
Artemether/ Lumefantrine (Coartem/Riamet)	Metabolism: Artemether and lumefantrine are both metabolized by CYP 3A4[12] Enzyme Induction: Artemether induces CYP 3A4 and 2C19[12] Enzyme Inhibition: Lumefantrine inhibits CYP 2D6[12] – unclear clinical significance	**Artemether: also see section on "Artemisinins"** **Lumefantrine:** Cardiotoxicity: No clinical adverse event attributable to QTc prolongation (e.g. syncope, sudden death) or dose related changes in ECG have been reported[53-59] Lumefantrine has the theoretical potential to cause QTc prolongation due to its chemical similarity to halofantrine,[12] although both Canadian[17] and WHO[2] guidelines for the treatment of malaria explicitly state that lumefantrine does not cause cardiotoxicity. The WHO guidelines go on to state that lumefantrine appears to be remarkably well tolerated and that there is no evidence that drug interactions lead to any clinically harmful effects. NNRTIs • **Nevirapine**: HIV-positive adults received 6-dose artemether/lumefantrine 80/480 mg before and at steady-state nevirapine. Coadministration resulted in significant reductions in artemether (61% ↓ Cmax, 72% ↓ AUC), dihydroartemisinin (45% ↓ Cmax, 37% ↓ AUC) and NVP

		(42% ↓ Cmax, 46% ↓ AUC) exposures, which is likely to increase risk of treatment failure. Alternative anti-malarials should be considered for HIV/malaria co-infected patients receiving nevirapine.[60] • In HIV-positive subjects on nevirapine-based treatment (n=18) or who were antiretroviral-naïve (n=18) received 6 doses of artemether-lumefantrine (80 mg/480 mg). Day 7 lumefantrine concentrations were significantly higher (86%) while median artemether and dihydroartemisinin AUC were significantly lower in the nevirapine vs. naïve subjects.[61] • Eleven HIV-positive subjects on nevirapine-based cART received artemether-lumefantrine 80/480 mg BID for 3 days. Compared to historical HIV-positive controls with similar body weight not on ART, artemether AUC was ↓ 65% and lumefantrine AUC was ↓ 60%, with a shorter t1/2 (1.6 vs 4.8 days, p<0.001).[62] • **Efavirenz:** HIV-positive adults received 6-dose artemether/lumefantrine 80/480 mg before and at steady-state efavirenz. Coadministration resulted in significant reductions in artemether (59% ↓ Cmax, 79% ↓ AUC), dihydroartemisinin (78% ↓ Cmax, 75% ↓ AUC), and lumefantrine (28% ↓ Cmax, 56% ↓ AUC) exposures, which is likely to increase risk of treatment failure. Efavirenz concentrations were not altered by artemether-lumefantrine. Alternative anti-malarials should be considered for HIV/malaria co-infected patients receiving efavirenz.[60] • In 12 healthy adult volunteers, coadministration of artemether/lumefantrine 80/480 mg BID alone and in the presence of steady-state efavirenz 600 mg resulted in ↓ AUC exposure for artemether, DHA, and lumefantrine of -51% (p=0.084), -46% (p=0.005), and -21% (p=0.102), respectively. Day 7 lumefantrine levels were 46% lower (p=0.002) with EFV, but lumefantrine half-life was unchanged. Efavirenz AUC was ↓ 17% (p=0.034) when coadministered with artemether/lumefantrine.[63] • **Etravirine:** in healthy volunteers, coadministration of etravirine 200 mg BID plus artemether 80/lumefantrine 480 mg resulted in 38% ↓ AUC artemether, 15% ↓ AUC dihydroartemisinin and 13% ↓ AUC of lumefantrine;

		etravirine pharmacokinetics were not affected. Coadministration of etravirine with artemether/lumefantrine may lower antimalarial activity of artemether; use combination with caution.[22, 64] PIs · **All (APV, ATZ, Darunavir, IDV, LPV, NFV, RTV, SQV, Tipranavir/RTV)**: ↑ lumefantrine plasma levels ↑ risk of toxicity (incl. QT prolongation) due to inhibition of CYP 3A4 by PIs. Concurrent use is not recommended by manufacturer[53]; others suggest may use with caution.[12] · **Lopinavir/ritonavir:** Co-administration of artemether/lumefantrine (AL) with steady-state LPV/RTV 400/100mg bid ↑ lumefantrine AUC 193% but treatment was well-tolerated in 10 subjects studied.[65] Lumefantrine levels were within the normal range of concentrations found in patients not on PIs (historical controls). Authors suggest no dosage adjustments required and that ↑ lumefantrine levels may be beneficial as lumefantrine exposure has been correlated with treatment response. In another study, 10 healthy volunteers received a standard, three-day course of AL with and without concomitant steady-state lopinavir/ritonavir 400/100mg bid.[66] In the presence of LPV/RTV, lumefantrine AUC ↑ 2-3 fold, there was a trend toward artemether Cmax and AUC ↓, and dihydroartemisinin (DHA, active artemether metabolite) Cmax and AUC decreased. DHA:artemether AUC ratios and LPV/RTV pharmacokinetics were not affected. Authors suggest that AL and LPV/RTV may be safely coadministered in patients with malaria and HIV, as lumefantrine AUC is a key parameter with respect to malarial cure and due to the excellent safety profile of AL. In an open-label, parallel study, HIV-positive patients who were ART-naïve or on stable LPVr received standard AL 80mg/480mg dosing for 3 days. Lumefantrine AUC was 9.3-fold higher in the LPVr arm vs. the non-ART arm, but an increase in adverse effects was not observed. Artemether and dihydroartemisinin concentrations were also significantly increased by LPVr, but to a lesser extent.[67]

		The kinetics of single-dose artemether/lumefantrine were investigated in HIV-infected subjects either on stable lopinavir/ritonavir-based therapy or who were treatment-naïve. In the presence of lopinavir/ritonavir, artemether Cmax ↓ 50%, AUC ↓ 43%, lumefantrine Cmax ↑ 280%, AUC ↑ 486%, and dihydroartemisinin kinetics were not significantly altered.[68] • **Darunavir/ritonavir**: in healthy volunteers, coadministration of darunavir 600/ritonavir 100 mg BID plus artemether 80/lumefantrine 480 mg resulted in 16% ↓ AUC artemether, 18% ↓ AUC dihydroartemisinin and 2.75-fold ↑ AUC of lumefantrine; darunavir and ritonavir pharmacokinetics were not affected. Darunavir/ritonavir and artemether/lumefantrine can be used without dose adjustments. However, the combination should be used with caution as increased lumefantrine exposure may increase the risk of QT prolongation. should not be coadministered.[34] Integrase inhibitor • **Elvitegravir/cobicistat**: potential for ↑in artemether and lumafantrine levels due to inhibition of CYP 3A4, and possible ↓ elvitegravir and cobicistat concentrations. This interaction has not been studied; avoid combination if possible.
Atovaquone/ Proguanil (Malarone)	Metabolism: *Atovaquone* is 94% eliminated unchanged in the feces; *proguanil* is 40-60% excreted unchanged by the kidneys, with the remainder metabolized by CYP 2C19 and CYP 3A4 to its more active metabolite, cycloguanil.[9]	NRTIs · **Zidovudine:** 33% ↑ in AUC of AZT (given as 200mg q8h) with atovaquone (given as 750mg bid).[69] *Likely not clinically significant for most patients, either for prophylaxis or treatment of malaria . Dosage modifications not recommended but may be considered in patients with evidence of bone marrow toxicity.[12] NNRTIs · **Efavirenz:** A recent study administered a single dose of Malarone™ to HIV+ individuals who had been taking EFV for at least one month.[70] AUC ↓~70% for atovaquone and 50% for proguanil compared with healthy volunteers. Decreases in atovaquone exposure have been associated with malaria treatment failure.[71] *Clinical significance unknown – study authors suggest taking Malarone™ with a high-fat meal and

		that dosage increase may be required for prophylaxis. Dosage increases may also be warranted for treatment in this setting. Another kinetic study in 15 healthy subjects found a 115% ↑ AUC of proguanil, and a 68% ↓ in the ratio of the active cycloguanil metabolite/parent drug. Cycloguanil Cmin was > MIC of most malaria strains, therefore a dosage adjustment was not empirically recommended.[72] Until further information on interaction is available, suggest avoiding co-administration if other options available. • **Etravirine:** Case report of a 32 year-old Caucasian female on maraviroc, raltegravir, etravirine and unboosted saquinavir who started atovaquone/proguanil prophylaxis; antiretroviral drug concentrations were measured at baseline and 20 days after initiation of atovaquone/proguanil. In the presence of atovaquone/ proguanil, a marked increase in etravirine and saquinavir concentrations (+55% and +274%, respectively) was observed. A slight decrease in raltegravir and maraviroc AUC0-12h (-23% and -9%, respectively), was also noted, but these changes were not considered clinically significant. No notable side effects were reported by the patient.[73] <u>PIs</u> · **Indinavir**: 23% ↓ in trough levels of unboosted IDV when combined with atovaquone.[74] Another study found 5% ↓ in IDV AUC and 13%↑ in atovaquone AUC with co-administration.[75] *Combination may be given together without dose adjustment.[12] • **Saquinavir:** Case report of a 32 year-old Caucasian female on maraviroc, raltegravir, etravirine and unboosted saquinavir who started atovaquone/proguanil prophylaxis; antiretroviral drug concentrations were measured at baseline and 20 days after initiation of atovaquone/proguanil. In the presence of atovaquone/ proguanil, a marked increase in etravirine and saquinavir concentrations (+55% and +274%, respectively) was observed. A slight decrease in raltegravir and maraviroc AUC0-12h (-23% and -9%, respectively), was also noted, but these changes were not considered clinically significant. No notable side effects were reported by the patient.[73] · **Lopinavir/ritonavir or ritonavir-containing regimens**: may

		↓ atovaquone plasma concentrations (likely due to enhanced glucuronyl transferase activity with RTV).[76] A recent study administered a single dose of Malarone™ to HIV+ individuals who had been taking LPV/RTV and ATV/RTV for at least one month.[70] In patients taking LPV/RTV, AUC ↓~70% for atovaquone and 50% for proguanil compared with healthy volunteers. In patients taking ATV/RTV, AUC ↓ 40-50% for atovaquone and 50% for proguanil. Decreases in atovaquone exposure have been associated with malaria treatment failure.[71] *Clinical significance unknown – study authors suggest taking Malarone™ with a high-fat meal and that Malarone™ dosage increase may be required for prophylaxis in patients taking LPV/RTV.[70] Dosage increases may also be required for treatment in this setting. Until further information on interaction is available, suggest avoiding co-administration if other options available. Integrase inhibitor • **Elvitegravir/cobicistat**: potential for increase in proguanil levels due to inhibition of CYP 3A4. This interaction has not been studied. Other · **Rifabutin**: A 34% ↓ in atovaquone AUC and a 19% ↓ in rifabutin AUC were observed when these drugs were used in combination.[74] ***Combination not recommended.**[12] · **Rifampin**: A 50% ↓ in atovaquone levels has been observed when used in combination with rifampin[74] ***Combination not recommended.**[12] · **Tetracycline**: A 40% ↓ in atovaquone plasma concentration has been observed when used with tetracycline.[74] Mechanism of interaction unknown. ***Combination not recommended** due to risk of therapeutic failure.
Pyrimethamine/ Sulfadoxine (Fansidar)	Metabolism: *Sulfadoxine* is metabolized in the liver via conjugation, acetylation and glucuronidation.[12] *Pyrimethamine* is hepatically metabolized.[9]	NRTIs · **Zidovudine**: risk of additive hematotoxicity when used in combination. * Monitor CBC and co-administer cautiously in patients already anemic. NNRTIs · **Nevirapine:** risk of severe adverse hepatic/cutaneous reactions with both medications. While the severe cutaneous reactions seen with Fansider™ in malaria prophylaxis have

		only rarely been observed with intermittent preventive treatment (IPT),[77] HIV infected individuals may be at greater risk of adverse reactions. *Recommend staggering the introduction of Fansidar™ and nevirapine by minimum 4 weeks if possible to reduce potential for diagnostic confusion should adverse events occur .[25] Nevirapine when given as a single dose in perinatal prophylaxis has not been associated with severe adverse effects in the mother.[25] PIs · **Ritonavir**: based on metabolism of drugs[9, 12] and lack of clinical evidence for interaction,[78] combination is likely safe to use. Other · **Co-trimoxazole**: ↑ risk of severe adverse skin (approximately 100-fold compared to HIV negative individuals)[79], hematologic and hepatic interactions[25] when used in combination. ***Avoid coadministration.** Suggest initiating co-trimoxazole at least 4 weeks after last sulfadoxine/pyrimethamine dose.[25] WHO suggests that pregnant women on cotrimoxazole prophylaxis should not receive intermittent preventive treatment (IPT) with Fansidar™ and that malarial illness in HIV-infected pregnant women who receive cotrimoxazole prophylaxis should be managed with antimalarial medicines that do not contain sulfonamides or sulfones.[2] Potential for *P. falciparum* cross-resistance between trimethoprim/sulfamethoxazole and sulfadoxine/pyrimethamine.[80, 81]

Dapsone/ Pyrimethamine (Maloprim or Deltaprim)	Metabolism: *Dapsone* >50% metabolized by N-acetyl-transferase to the active metabolite monoacetyl-dapsone, with the remainder metabolized via CYP 3A4-mediated hydroxylation.[9]	NRTIs · **Zidovudine**: potential for additive hematological adverse effects when used in combination.[12, 82] *Combination not recommended. Monitor CBC if combination therapy necessary. Screening for glucose-6- phosphate-dehydrogenase deficiency prior to use may decrease risk of some hematological toxicity. · **Stavudine**: potential for increased risk of peripheral neuropathy due to overlapping toxicity profiles.[83] *Avoid combination if other options available. PIs · **All protease inhibitors:** potential ↑ dapsone plasma levels and risk of toxicity due to inhibition of CYP 3A4..[84,] As metabolism of dapsone is primarily via N-acetylation, clinically significant interactions are unlikely but cannot be excluded.[12] * Monitor for adverse effects, especially hematological, if combination therapy necessary. · **Tipranavir** (unboosted): potential for ↓ dapsone exposure via CYP3A induction Integrase inhibitor • **Elvitegravir/cobicistat**: potential for ↑ dapsone levels due to inhibition of CYP 3A4. This interaction has not been studied. Other · **Rifabutin**: potential ↓ dapsone effectiveness due to induction of dapsone metabolism. Manufacturer suggests dapsone dosage increases may be necessary.[85] However, given that Maloprim™ and Deltaprim™ are fixed-dose combination products with a low dose of dapsone given once weekly, use in combination with rifabutin for malaria prophylaxis should likely be avoided. · **Rifampin**: 7-10-fold ↓ dapsone levels have been observed when used in combination with rifampin.[86] Dapsone dose adjustment is not required in the context of leprosy treatment.[12] However, dapsone doses for malaria prophylaxis are much lower and rifampin doses much higher for the treatment of TB than used in leprosy treatment *Avoid combination. · **Co-trimoxazole**: potential for additive hematological adverse effects, including megaloblastic anemia[87] when used with

		dapsone and/or pyrimethamine.[12, 88] *Combination not recommended. Monitor CBC closely if using in combination.[12]
Trimethoprim/ Sulfamethoxazole (Co-trimoxazole, Septra, Septrin)	Metabolism: *Trimethoprim* 60% excreted unchanged by the kidney, and the rest is metabolized in the liver.[8] *Sulfamethoxazole* is metabolized in the liver by acetylation and glucuronidation.[8] Enzyme Inhibition: both trimethoprim and sulfamethoxazole may have inhibitory effects on CYP 2C9.[8]	NRTIs · **Lamivudine (3TC):** combination may ↓ lamivudine clearance.[89] *Not clinically significant.[90] · **Zidovudine:** potential for additive hematological toxicity when used in combination. *Combination used commonly in clinical practice. Monitor CBC when using combination. NNRTIs · **Nevirapine**: potential for severe skin reactions if initiated concurrently; space initiation of TMP-SMX/NVP by 2-4 weeks if possible.[25] Other · **Rifabutin**: Induction of sulfamethoxazole metabolism by rifabutin ↑ exposure to the sulfamethoxazole toxic metabolite, sulfamethoxazole hydroxylamine (↑AUC 50%).[91] *Monitor for adverse dermatologic, hematologic, and hepatic effects when using in combination. · **Sulfadoxine/Pyrimethamine:** ↑ risk of severe adverse skin (approximately 100-fold compared to HIV negative individuals)[67], hematologic and hepatic interactions[25] when used in combination. ***Avoid coadministration as compounds have very similar activity and toxicity profiles.** Suggest initiating co-trimoxazole at least 4 weeks after last sulfadoxine/pyrimethamine dose.[25] WHO suggests that pregnant women on cotrimoxazole prophylaxis should not receive intermittent preventive treatment (IPT) with Fansidar™ and that malarial illness in HIV-infected pregnant women who receive cotrimoxazole prophylaxis should be managed with antimalarial medicines that do not contain sulfonamides or sulfones.[2] Potential for *P. falciparum* cross-resistance between trimethoprim/sulfamethoxazole and sulfadoxine/pyrimethamine.[80, 81]

Abbreviations: **APV** amprenavir; **ATV** atazanavir; **AUC** area under the plasma concentration versus time curve; **AZT** zidovudine; **CBC** complete blood count; **Cmin** minimum plasma concentration; **CYP** cytochrome P450; **EFV** efavirenz; **IDV** indinavir; **LPV** lopinavir; **NNRTI** non-nucleoside reverse transcriptase inhibitor; **NRTI** nucleoside reverse transcriptase inhibitor; **NFV** nelfinavir; **NVP** nevirapine; **PI** protease inhibitor; **PJP** pneumocystis jirovecii pneumonia; **PK** pharmacokinetic; **RTV** ritonavir; **SQV** saquinavir

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