

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

Antimalarial Agent (Brand)	Pharmacokinetic Characteristics	Relevant HIV Drug Interactions *Suggested Management
<i>Quinine Derivatives</i>		
Amodiaquine (Camoquin, Flavoquine)	<u>Metabolism:</u> 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.	<p><u>NRTI</u></p> <ul style="list-style-type: none"> · 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. <p><u>NNRTI</u></p> <ul style="list-style-type: none"> · 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. <p><u>PIs</u></p> <ul style="list-style-type: none"> · SQV, LPV, TPV,⁴ high-dose RTV⁶ were potent CYP 2C8 inhibitors in vitro at clinically relevant concentrations which may increase the risk of amodiaquine adverse effects if coadministered.
Chloroquine (Aralen)	<u>Metabolism:</u> 50% excreted renally unchanged; CYP 3A4 and 2D6 metabolize to active metabolites mono- and bis-desethyl chloroquine. ⁷	<p><u>PIs</u></p> <ul style="list-style-type: none"> · Saquinavir: one in vitro study suggested antagonistic HIV effects between chloroquine and SQV,⁹ however, another found a synergistic anti-HIV effect between the two drugs.¹⁰ Clinically

	<p><u>Enzyme Inhibition:</u> some CYP 2D6; however, effect less pronounced in vivo⁸</p>	<p>significant effects unlikely.¹¹</p> <ul style="list-style-type: none"> • Ritonavir: potential for increase in chloroquine levels due to inhibition of CYP 3A4 and 2D6. This interaction has not been studied.¹¹ <p><u>Other</u></p> <ul style="list-style-type: none"> • Co-trimoxazole: potential increased risk of cardiotoxicity (QT-interval prolongation) when used concurrently.^{12,13} Theoretical interaction, unlikely to be clinically significant.
Mefloquine (Lariam)	<p><u>Metabolism:</u> via CYP 3A4 to inactive carboxy metabolite^{8,12}</p>	<p>*Avoid use in treatment in pregnancy¹⁴ and in prophylaxis in 1st trimester of pregnancy (↑ risk of spontaneous abortion¹⁵) 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.^{16,17}</p> <p><u>NNRTIs</u></p> <p>Potential for ↓ mefloquine levels due to CYP 3A induction</p> <p><u>PIs</u></p> <ul style="list-style-type: none"> • Ritonavir: 31% ↓ in AUC and 43% ↓ in Cmin of ritonavir after multiple concurrent dosing; mefloquine pharmacokinetics unchanged¹⁸. *Likely safe to co-administer without dose adjustments.¹¹ • 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.¹⁹ Levels of the PIs and mefloquine were therapeutic and no side effects were reported. • Tipranavir (unboosted): Potential for ↓ mefloquine levels due to CYP3A induction <p><u>Other</u></p> <ul style="list-style-type: none"> • 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.²⁰ *Study authors recommend avoiding simultaneous use of rifampin and mefloquine.
Quinine	<p><u>Metabolism:</u> via CYP 3A4 (minor contribution from 2C19) to active metabolite 3-hydroxyquinine (toxic); also 20% excreted renally unchanged⁸</p>	<p><u>NNRTIs</u></p> <ul style="list-style-type: none"> • Efavirenz and etravirine may ↓ quinine exposure to subtherapeutic range due to induction of CYP 3A4.^{11,21} *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

		<p>14 patients on and off steady-state nevirapine 200mg bid.²² 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.</p> <p><u>PIs</u></p> <ul style="list-style-type: none"> • 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.^{12,23} Consider therapeutic drug monitoring of quinine if possible with maintenance dose-adjustment as necessary. • Ritonavir: Ten healthy volunteers on steady-state ritonavir 200mg bid received a single dose of quinine 600 mg.²⁴ 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. <p><u>Other</u></p> <ul style="list-style-type: none"> • 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).²⁵ Quinine dose should probably be increased in patients already receiving rifampin for treatment of TB.²³
<p>Quinidine (Qualaquin, Quindex, others)</p>	<p><u>Metabolism:</u> via CYP 3A4</p> <p><u>Enzyme Inhibition:</u> Potent inhibitor of CYP 2D6⁸</p>	<p><u>NNRTIs</u></p> <ul style="list-style-type: none"> • Nevirapine, efavirenz, etravirine: potential for ↓ quinidine concentration and therapeutic failure. *Caution warranted; therapeutic drug monitoring recommended if available.^{11,21}

		<p><u>PIs</u></p> <ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> → Contraindicated by manufacturer: in combination with NFV, RTV, SQV, tipranavir/RTV^{26,27,28,29} → Combination cautioned by manufacturer: ATV, darunavir, IDV, LPV/RTV^{30,31,32,33} • 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. <p><u>Other</u></p> <ul style="list-style-type: none"> • Rifampin: ↓ quinidine plasma levels and effectiveness via induction of CYP 3A4^{34,35}. *Consider quinidine dose increase if using concurrently – monitor quinidine plasma levels if possible.¹²
Artemisinins		
Artemisinin	<p><u>Metabolism:</u> primarily via CYP 2B6, with CYP 3A4 likely playing a role in patients with decreased CYP 2B6 activity, to inactive metabolites^{8,36}</p> <p><u>Enzyme Induction:</u> may induce CYP 2C19⁸</p>	<p>*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.³⁷ Some reports of potential embryotoxicity and morphological abnormalities in animal studies,³⁸ however, in almost 1000 documented cases of exposures during pregnancy, no adverse pregnancy effects on the mother or fetus have been reported.³⁹</p> <p><u>NNRTIs:</u> potential ↓ in artemisinin levels due to CYP 2B6 induction</p> <p><u>PIs:</u> potential ↓ in artemisinin levels due to induction of CYP 2B6 by ritonavir; In vitro study suggesting potential antagonism of artemisinin endoperoxide activity vs. <i>P. falciparum</i> when combined with PIs (studied PIs included RTV, SQV, IDV). Clinical significance is unknown, however caution is warranted with artemisinin monotherapy and PIs.⁴⁰</p>
Dihydroartemisinin	<p><u>Metabolism:</u> unclear, likely metabolized in the liver by glucuronidation and eliminated via biliary and renal excretion⁸</p>	<p>*Pregnancy see artemisinin entry</p> <p>Nelfinavir, ritonavir, tipranavir: Caution may be warranted when using with dihydroartemisinin as these PIs may induce glucuronyltransferase activity.</p>
Artemether	<p><u>Metabolism:</u> via CYP 3A4/5 to active</p>	<p>*Pregnancy see artemisinin entry</p>

	<p>metabolite dihydroartemisinin (more potent antimalarial than parent compound)¹¹</p> <p><u>Enzyme Induction:</u> CYP 3A4 and CYP 2C19¹¹</p> <p><u>Enzyme Inhibition:</u> potential CYP 1A2 inhibition⁴¹</p>	<p>All PIs (see artemether/lumefantrine and artemisinin entries)</p> <ul style="list-style-type: none"> potential ↓ in artemether's conversion to active metabolite via CYP 3A4 inhibition. *Likely not clinically significant, as parent also active, but data lacking.¹¹ <p>NNRTIs</p> <ul style="list-style-type: none"> 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.¹¹
Artesunate (Arzuna)	<p><u>Metabolism:</u> rapidly metabolized to dihydroartemisinin (active form) in vivo, then glucuronidated.⁸</p>	<p>*Pregnancy see artemisinin entry</p>
8-Aminoquinolines		
Primaquine	<p><u>Metabolism:</u> via CYP 1A2, 2D6, 3A4⁴², to inactive carboxyprimaquine. Non-CYP-mediated oxidative processes may also play an important role in metabolism.⁸</p>	<p>*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 delivery¹⁶</p> <p>NRTIs</p> <ul style="list-style-type: none"> Zidovudine: both drugs may cause hematotoxicity^{12,43} 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. <p>NNRTIs/Pis</p> <p>As multiple metabolic pathways are involved in primaquine metabolism, drug interactions are difficult to predict. No published reports of interactions with NNRTIs/Pis</p>
Halofantrine		
Halofantrine (Halofan)	<p><u>Metabolism:</u> via CYP 3A4 to active metabolite N-desbutylhalofantrin (parent compound has a narrow therapeutic window and is cardiotoxic)⁸</p>	<p>Contraindicated in pregnancy⁴⁴</p> <p>Food - Ingestion with food, especially when high in fat, markedly increases serum levels</p> <p>NNRTIs</p> <ul style="list-style-type: none"> Efavirenz, etravirine, nevirapine: halofantrine has a narrow therapeutic index and potential inhibition¹¹ 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. <p>Pis</p> <ul style="list-style-type: none"> 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. ¹¹ Avoid combination.
Antibiotics		
Clindamycin (Dalacin C)	<u>Metabolism:</u> via CYP 3A4 ⁴⁵	None known
Doxycycline (Vibramycin)	<u>Metabolism:</u> Not fully elucidated. May be metabolized in the liver, excreted unchanged in urine and bile or partially deactivated in the intestine by chelate formation ^{12,46}	<p>Contraindicated in pregnancy</p> <p><u>NNRTIs, PIs:</u></p> <ul style="list-style-type: none"> 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.⁴⁷ <p><u>Other</u></p> <ul style="list-style-type: none"> 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.⁴⁸ *Avoid combination for malaria prophylaxis if possible. Monitor closely for therapeutic efficacy of doxycycline if using in combination.
Tetracycline (Achromycin)	<u>Metabolism:</u> none; excreted unchanged in urine and bile ¹²	<p>Contraindicated in pregnancy</p> <p>No known drug interactions with antiretrovirals</p>
Combination Antimalarials		
Artemether/ Lumefantrine (Coartem/Riamet)	<p><u>Metabolism:</u> Artemether and lumefantrine are both metabolized by CYP 3A4¹¹</p> <p><u>Enzyme Induction:</u> Artemether induces CYP 3A4 and 2C19¹¹</p> <p><u>Enzyme Inhibition:</u> Lumefantrine inhibits CYP 2D6¹¹ – unclear clinical significance⁸</p>	<p>Artemether: also see section on “Artemisinins”</p> <p>Lumefantrine:</p> <p><u>Cardiotoxicity:</u> No clinical adverse event attributable to QTc prolongation (e.g. syncope, sudden death) or dose related changes in ECG have been reported^{49,50,51,52,53,54,55} Lumefantrine has the theoretical potential to cause QTc prolongation due to its chemical similarity to halofantrine,¹¹ although both Canadian¹⁶ and WHO⁵⁶ 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.</p> <p><u>NNRTIs</u></p> <ul style="list-style-type: none"> Efavirenz, etravirine, nevirapine: potential inhibition¹¹ or induction of CYP 3A4 by NNRTIs may ↑ toxicity or ↓ efficacy of lumefantrine.

		<p>Clinically, induction of CYP 3A4 generally prevails with NNRTIs. Drug interaction may not be clinically significant⁵²</p> <p><u>PIs</u></p> <ul style="list-style-type: none"> • All (APV, ATZ, Darunavir, IDV, LPV, NFV, RTV, SQV, Tipranavir/RTV): ↑ lumefantrine plasma levels ↑ risk of toxicity due to inhibition of CYP 3A4 by PIs. Concurrent use is contraindicated by manufacturer⁴⁷ but others suggest may use with caution,¹¹ or that the drug interaction may not be clinically significant^{52,53} • 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.⁵⁷ Lumefantrine levels were within the normal range of concentrations found in patients not on PIs in another study.⁴⁸ Authors suggest no dosage adjustments required and that ↑ lumefantrine levels may be beneficial as lumefantrine exposure has been correlated with treatment response.⁵¹ <p>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.⁵⁸ 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.</p>
<p>Atovaquone/ Proguanil (Malarone)</p>	<p><u>Metabolism:</u> 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.⁸</p>	<p><u>NRTIs</u></p> <ul style="list-style-type: none"> • Zidovudine: 33% ↑ in AUC of AZT (given as 200mg q8h) with atovaquone (given as 750mg bid).⁵⁹ *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.^{11,12} <p><u>NNRTIs</u></p> <ul style="list-style-type: none"> • Efavirenz: A recent study administered a single dose of Malarone™ to HIV+ individuals who had been taking EFV for at least one month.⁶⁰ AUC ↓~70% for atovaquone and 50% for proguanil compared with healthy volunteers. Decreases in atovaquone exposure have been associated with malaria treatment failure.⁶¹ <p>*Clinical significance unknown – study authors suggest taking</p>

		<p>Malarone™ with a high-fat meal and that dosage increase may be required for prophylaxis.⁵⁸ 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 C_{min} was > MIC of most malaria strains, therefore a dosage adjustment was not empirically recommended.⁶² Until further information on interaction is available,⁶³ suggest avoiding co-administration if other options available.</p> <p><u>PIs</u></p> <ul style="list-style-type: none"> • Indinavir: 23% ↓ in trough levels of unboosted IDV when combined with atovaquone.⁶⁴ Another study found 5% ↓ in IDV AUC and 13% ↑ in atovaquone AUC with co-administration.⁶⁵ *Combination may be given together without dose adjustment¹¹ • Lopinavir/ritonavir or ritonavir-containing regimens: may ↓ atovaquone plasma concentrations (likely due to enhanced glucuronyl transferase activity with RTV).^{27,33,66} <p>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.⁵⁸ 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.⁶⁷</p> <p>*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.⁵⁸ Dosage increases may also be required for treatment in this setting. Until further information on interaction is available,⁶⁰ suggest avoiding co-administration if other options available.</p> <p><u>Other</u></p> <ul style="list-style-type: none"> • Rifabutin: A 34% ↓ in atovaquone AUC and a 19% ↓ in rifabutin AUC were observed when these drugs were used in combination.⁶¹ *Combination not recommended.¹² • Rifampin: A 50% ↓ in atovaquone levels has been observed when used in combination with rifampin⁶¹ *Combination not recommended.¹² • Tetracycline: A 40% ↓ in atovaquone plasma concentration has been observed when used with tetracycline.⁶¹ Mechanism of interaction unknown. *Combination not recommended due to
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<p>Pyrimethamine/ Sulfadoxine (Fansidar)</p>	<p><u>Metabolism:</u> <i>Sulfadoxine</i> is metabolized in the liver via conjugation, acetylation and glucuronidation.¹² <i>Pyrimethamine</i> is hepatically metabolized.⁸</p>	<p>risk of therapeutic failure.</p> <p><u>NRTIs</u></p> <ul style="list-style-type: none"> • Zidovudine: risk of additive hematotoxicity when used in combination. * Monitor CBC and co-administer cautiously in patients already anemic.²³ <p><u>NNRTIs</u></p> <ul style="list-style-type: none"> • Nevirapine: risk of severe adverse hepatic/cutaneous reactions with both medications. While the severe cutaneous reactions seen with Fansidar™ in malaria prophylaxis have only rarely been observed with intermittent preventive treatment (IPT),⁶⁸ HIV infected individuals may be at greater risk of adverse reactions.⁴³ *Recommend staggering the introduction of Fansidar™ and nevirapine by minimum 4 weeks if possible to reduce potential for diagnostic confusion should adverse events occur.²³ Nevirapine when given as a single dose in perinatal prophylaxis has not been associated with severe adverse effects in the mother.²³ <p><u>PIs</u></p> <ul style="list-style-type: none"> • Ritonavir: one author suggests caution with coadministration,¹¹ however, based on metabolism of drugs^{8,12} and lack of clinical evidence for interaction,⁶⁹ combination is likely safe to use. <p><u>Other</u></p> <ul style="list-style-type: none"> • Co-trimoxazole: ↑ risk of severe adverse skin (approximately 100-fold compared to HIV negative individuals)⁷⁰, hematologic and hepatic interactions²³ when used in combination. *Avoid coadministration. Suggest initiating co-trimoxazole at least 4 weeks after last sulfadoxine/pyrimethamine dose.²³ 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 <i>P. falciparum</i> cross-resistance between trimethoprim/sulfamethoxazole and sulfadoxine/pyrimethamine^{71,72}
<p>Dapsone/ Pyrimethamine (Maloprim or Deltaprim)</p>	<p><u>Metabolism:</u> <i>Dapsone</i> >50% metabolized by N-acetyl-transferase to the active metabolite monoacetyl-dapsone, with the remainder metabolized via CYP 3A4-mediated hydroxylation.⁸</p>	<p><u>NRTIs</u></p> <ul style="list-style-type: none"> • Zidovudine: potential for additive hematological adverse effects when used in combination.^{11,73} *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.

		<ul style="list-style-type: none"> • Stavudine: potential for increased risk of peripheral neuropathy due to overlapping toxicity profiles.⁷⁴ *Avoid combination if other options available. <p><u>PIs</u></p> <ul style="list-style-type: none"> • All protease inhibitors: potential ↑ dapsone plasma levels and risk of toxicity due to inhibition of CYP 3A4.^{27,75} As metabolism of dapsone is primarily via N-acetylation, clinically significant interactions are unlikely but cannot be excluded.^{11,12} * Monitor for adverse effects, especially hematological, if combination therapy necessary. • Tipranavir (unboosted): potential for ↓ dapsone exposure via CYP3A induction <p><u>Other</u></p> <ul style="list-style-type: none"> • Rifabutin: potential ↓ dapsone effectiveness due to induction of dapsone metabolism. Manufacturer suggests dapsone dosage increases may be necessary.⁷⁶ 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.⁷⁷ 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 anemia⁷⁸ when used with dapsone and/or pyrimethamine.^{11,74,79} *Combination not recommended. Monitor CBC closely if using in combination.¹²
<p>Trimethoprim/ Sulfamethoxazole (Co-trimoxazole, Septra, Septrin)</p>	<p><u>Metabolism:</u> <i>Trimethoprim</i> 60% excreted unchanged by the kidney, and the rest is metabolized in the liver.⁸ <i>Sulfamethoxazole</i> is metabolized in the liver by acetylation and glucuronidation.⁸</p> <p><u>Enzyme Inhibition:</u> both trimethoprim and sulfamethoxazole may have inhibitory effects on CYP 2C9.⁸</p>	<p><u>NRTIs</u></p> <ul style="list-style-type: none"> • Lamivudine (3TC): combination may ↓ lamivudine clearance.⁸⁰ *Not clinically significant.⁸¹ • Zidovudine: potential for additive hematological toxicity when used in combination.² *Combination used commonly in clinical practice. Monitor CBC when using combination. <p><u>NNRTIs</u></p> <ul style="list-style-type: none"> • Nevirapine: potential for severe skin reactions if initiated concurrently; space initiation of TMP-SMX/NVP by 2-4 weeks if possible.²³ <p><u>Other</u></p>

		<ul style="list-style-type: none"> • Rifabutin: Induction of sulfamethoxazole metabolism by rifabutin ↑ exposure to the sulfamethoxazole toxic metabolite, sulfamethoxazole hydroxylamine (↑AUC 50%).⁸² *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 interactions²³ 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.²³ 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 <i>P. falciparum</i> cross-resistance between trimethoprim/sulfamethoxazole and sulfadoxine/pyrimethamine.^{68,69}
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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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