TABLE 8. Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections*

Drugs	Interacting with	Mechanism/effects	Recommendations
Acyclovir	Probenecid (with cidofovir)	Probenecid might decrease renal clearance of acyclovir by 32%, increasing acyclovir area under the concentration curve (AUC)	No dosage adjustment; monitor for acyclovir toxicities
Atovaquone	Rifabutin	Atovaquone concentration (conc.) decreases by 34%; Rifabutin conc. Decreases by 19%	This combination should be avoided
	Rifampin	Atovaquone conc. decreases by 52%; Rifampin conc. increases by 37%	This combination should be avoided
	Tetracycline	Atovaquone conc. Decreases by 40%	This combination should be avoided; interaction study with doxycycline not available
	Zidovudine	Zidovudine AUC increases by 31%, possibly because of atovaquone inhibition of zidovudine glucuronidation	No dosage adjustment recommended, monitor for zidovudine toxicities
Caspofungin	Efavirenz, nevirapine, nelfinavir	Possible decreases in caspofungin conc. based on regression analyses of patient pharmacokinetic data; no formal pharmacokinetic study available at this time	Manufacturer recommends considering increasing maintenance dose of caspofungin to 70 mg/day when co-administered with the interacting drugs
	Rifampin	Caspufungin conc. decreases by 30%	Caspofungin dose should be increased to 70 mg/day
Cidofovir (plus probenecid)	Acyclovir, cephalosporins, dapsone, fluoroquinolones, ganciclovir, penicillins, valacyclovir, valganciclovir, zalcitabine, zidovudine,	Probenecid might decrease renal clearance of these drugs, increasing plasma conc.	Because of the infrequent dosing of probenecid when used with cidofovir, no dosage adjustment is necessary for interacting drugs; monitor for dose-related toxicities
Ciprofloxacin	Didanosine buffered formulations	Decreased ciprofloxacin absorption attributed to chelation with magnesium-aluminum buffer	Administer didanosine buffered preparation at least 2 hours after or 6 hours before ciprofloxacin
	Cidofovir plus Probenecid	Probenecid might reduce renal clearance of ciprofloxacin, increasing plasma conc.	No dosage adjustment necessary; monitor for ciprofloxacin toxicities
Clarithromycin	Atazanavir	Atazanavir minimum concentration (Cmin) increased 91%; Clarithromycin AUC increased 94%	Because of concerns about QT prolongation, decrease clarithromycin dose 50% or use alternative agent
CYP 3A4 Inhibitor and Substrate	Delavirdine	Delavirdine AUC increased 44%; clarithromycin AUC increased 100% and 14-OH clarithromycin AUC decreased 75%	No dosage adjustment recommended; might consider clarithromycin dose adjustment in patients with renal insufficiency; monitor for clarithromycin toxicities; or switch to azithromycin
	Efavirenz	Clarithromycin AUC decreased 39%; 14-OH clarithromycin AUC increased 34%	Significance unknown, no dosage adjustment recommended; some clinicians recommend switching to azithromycin
	Itraconazole	Possible bi-directional CYP 3A4 inhibition and increased AUC of both drugs	Monitor for toxicities of both itraconazole and clarithromycin
	Lopinavir/ritonavir (Kaletra®)	Increased clarithromycin AUC and decrease in 14-OH clarithromycin AUC	No dosage change in patients with normal renal function. ***CrCl (mL/min)*** — ***Clarithromycin*** 30–60 — decrease dose 50% <30 — decrease dose 75%
	Rifabutin	Clarithromycin AUC decreased by 44%; rifabutin AUC increased 76%–99%	Might need clarithromycin dose increase and decrease rifabutin dose; might result in increased rifabutin toxicities; some recommend use of azithromycin in place of clarithromycin
	Rifampin	Decreased mean clarithromycin conc. by 87%	This combination should be avoided; consider switching to azithromycin
	Ritonavir	Clarithromycin AUC increased 77% and decrease in 14-OH clarithromycin AUC	No dosage change in patients with normal renal function. ***CrCl (mL/min)*** — ***Clarithromycin*** 30–60 — decrease dose 50% <30 — decrease dose 75%
	Trimetrexate	Might increase trimetrexate AUC	No formal study performed; avoid concomitant use or monitor for trimetrexate toxicities
Dapsone	Rifampin	Decreased dapsone level 7–10-fold and dapsone t1/2 decreased from 24 to 11 hours	Reduced dapsone activities; might consider increasing dapsone dose or use alternative agent

TABLE 8. (*Continued*) Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections*

Drugs	Interacting with	Mechanism/effects	Recommendations
Doxycycline	Atovaquone	Tetracycline decreased atovaquone conc. 40%; effect of doxycycline on atovaquone unknown	Until doxycycline-atovaquone interaction data become available, avoid this combination if possible
	Didanosine buffered formulations	Decreased doxycycline absorption attributed to chelation with magnesium-aluminum buffer	Separate doxycycline with didanosine by at least 2 hours or use didanosine enteric-coated capsule
	Rifampin	Decreased doxycycline clearance, decreased t1/2 and AUC	Potential for decreased doxycycline efficacy; monitor closely for therapeutic failure
Erythromycin	Itraconazole	Potential for bi-directional inhibition of hepatic metabolism and increased serum conc. of both	Monitor for toxicities of both drugs
CYP 3A4 Inhibitor	Nevirapine	Nevirapine conc. increased by 100% compared with historic control	Recommended monitor for nevirapine toxicity
	Trimetrexate	Might increase trimetrexate AUC	No formal study performed; avoid concomitant use or monitor for trimetrexate toxicities
Fluconazole	Rifabutin	Rifabutin AUC increased 80%; no effect on fluconazole levels	Monitor for rifabutin toxicity or might consider dose reduction to 150 mg/day
CYP 3A4 inhibitor	Rifampin	Fluconazole AUC decreased by 23%–56%; no change in rifampin conc.	May need to increase fluconazole dose
	Trimetrexate	Might increase trimetrexate AUC	No formal study performed; avoid concomitant use or monitor for trimetrexate toxicities
	Zidovudine	Fluconazole decreased glucuronidation of zidovudine; fluconazole 400 mg/day results in increased zidovudine AUC by 74%	Monitor for zidovudine toxicities
Ganciclovir	Didanosine buffered formulations (study with enteric coated didanosine has not been done)	Didanosine AUC increased 78% with IV ganciclovir and increased 111% with oral ganciclovir	Might consider reducing didanosine dose; monitor for didanosine toxicities
	Cidofovir + Probenecid	Probenecid might decrease ganciclovir clearance and increase ganciclovir conc.	Because of the infrequent dosing of probenecid when used with cidofovir, no dosage adjustment is necessary; monitor for dose-related toxicities
Itraconazole	Clarithromycin	Potential for bi-directional inhibition of CYP3A4 metabolism with increased AUC of itraconazole and/or interacting drug(s)	Monitor for toxicities of clarithromycin; monitor itraconazole level and toxicities
CYP 3A4 Inhibitor and substrate	Delavirdine	Potential for bi-directional inhibition of CYP3A4 metabolism with increased AUC of itraconazole and/or delavirdine	Monitor for toxicities of delavirdine; monitor itraconazole level and toxicities
	Didanosine buffered preparation	Might decrease itraconazole oral absorption because of increased gastric pH from antacid in the didanosine preparation	Administer itraconazole at least 2–4 hours before didanosine buffered tablets, use didanosine enteric coated capsule, or take itraconazole with cola beverage to decrease gastric pH
	Efavirenz	No interaction study reported; potential induction or inhibition of itraconazole metabolism with increase or decrease in itraconazole AUC	Monitor itraconazole level and adjust dose accordingly
	Erythromycin	Potential for bi-directional inhibition of CYP3A4 metabolism with increased AUC of itraconazole and/or erythromycin	Monitor for toxicities of erythromycin; monitor itraconazole level and toxicities
	Nevirapine	Potential for induction of itraconazole metabolism and decrease in itraconazole conc.	Monitor itraconazole level and adjust according; monitor therapeutic efficacy
	Protease inhibitors other than ritonavir	Potential for bi-directional inhibition of CYP3A4 metabolism with increased AUC of itraconazole and/or protease inhibitors	Monitor for toxicities of protease inhibitors; monitor itraconazole level and toxicities (especially in patients with ritonavir-boosted protease inhibitor regimens)
	Rifabutin	Decrease in itraconazole conc. by 70%; potential for inhibition of rifabutin metabolism and increased rifabutin conc.	Avoid concomitant use if possible; if the combination is to be used, monitor itraconazole level and adjust dose accordingly; monitor for rifabutin toxicity

TABLE 8. (*Continued*) Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections*

Drugs	Interacting with	Mechanism/effects	Recommendations
Itraconazole (*Continued*)	Rifampin	Itraconazole AUC decreased 64%–88%; no change in rifampin conc.	Avoid concomitant use if possible. If the combination is to be used, monitor itraconazole level and adjust dose accordingly; monitor therapeutic response
CYP 3A4 Inhibitor and substrate	Ritonavir	Potential for substantial increase in itraconazole conc.	Might require reduced itraconazole dose; monitor itraconazole level and toxicities
	Trimetrexate	Itraconazole might substantially increase trimetrexate level because of inhibition of CYP3A4 metabolism	Monitor for trimetrexate toxicities
Ketoconazole	Amprenavir	Amprenavir AUC increased 31%; ketoconazole AUC increased 44%	Monitor for toxicities of each drug
CYP 3A4 Substrate	Delavirdine	Delavirdine Cmin increased 50%	Monitor for delavirdine toxicities
	Didanosine buffered formulations	Might decrease oral absorption of ketonconazole because of increased gastric pH from antacid in the didanosine preparation	Space apart doses of ketoconazole and didanosine by at least 2 hours or administer ketoconazole with cola beverage to decrease pH
	Indinavir	Indinavir AUC increased 68%; no substantial change in ketocoazole conc.	Decrease indinavir dose to 600 mg every 8 hours
	Lopinavir/ritonavir (Kaletra®)	Ketoconazole AUC increased threefold; no substantial change in lopinavir pharmacokinetics	Decrease ketoconazole dose and monitor for toxicities
	Nevirapine	Ketoconazole AUC decreased 63%; nevirapine AUC increased 15%–30%	Consider alternative antifungal or monitor for ketoconazole efficacy
	Rifabutin	Possible increase in rifabutin conc. and decrease in ketoconazole conc.	Monitor for rifabutin toxicities and ketoconazole efficacy
	Rifampin	Ketoconazole levels decreased 50%;	Avoid concomitant use if possible; consider alternative antifungal and/or antimycobacterial agent(s)
	Ritonavir	Ketoconazole AUC increased 3.4-fold	Ketoconazole dose >200 mg/day not recommended; monitor for ketoconazole toxicities
	Trimetrexate	Ketoconazole might substantially increase trimetrexate level because of inhibition of CYP3A4 metabolism	Monitor for trimetrexate toxicities
Pyrazinamide	Zidovudine	Decreased pyrazinamide conc. in one study	Monitor therapeutic efficacy or consider monitoring pyrazinamide level
Ribavirin	Didanosine	Increased intracellular levels of dideoxyadenosine triphosphate (ddA-TP)	This combination should be avoided; increased didanosine (ddI)-associated mitochondrial toxicities; if used together, monitor for toxicities (lactic acidosis, pancreatitis, peripheral neuropathy)
	Zidovudine	Decreased intracellular activities of zidovudine against HIV in vitro	Potential for worsening of HIV suppression; monitoring HIV viral load
Rifabutin	Amprenavir	Rifabutin AUC increased 193%; no change in amprenavir conc.	Decrease rifabutin dose by 50% (to 150 mg/day or 300 mg TIW)
CYP 3A4 Inducer and substrate	Atazanavir	Rifabutin AUC increased 210%; Cmin increased 343%; minimal change in atazanavir pharmacokinetics	Decrease rifabutin dose by 75% (to 150 mg every other day or three times weekly)
	Atovaquone	Atovaquone conc. decreased 34%; rifabutin conc. Decreased 19%	This combination should be avoided
	Clarithromycin	Rifabutin AUC increased 76% because of inhibition of hepatic metabolism; clarithromycin AUC might be reduced	Consider reducing rifabutin dose; monitor for rifabutin toxicities, or switching macrolide to azithromycin
	Delavirdine	Delavirdine AUC decreased 80%; rifabutin AUC increased 100%	This combination should be avoided
	Didanosine buffered formulation	Decreased rifabutin oral absorption	Space rifabutin and didanosine buffered formulation apart by at least 2 hours or use enteric coated didanosine capsule
	Efavirenz	Rifabutin AUC decreased 38%; no change in efavirenz conc.	Increase rifabutin dose to 450 mg/day or 600 mg two to three times weekly; effect of efavirenz and protease inhibitor(s) on rifabutin conc. has not been studied

TABLE 8. (*Continued*) Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections*

Drugs	Interacting with	Mechanism/effects	Recommendations
Rifabutin (*Continued*)	Fluconazole	Rifabutin AUC increased 80% because of inhibition of hepatic metabolism	Consider reducing rifabutin dose or monitor for rifabutin toxicities
CYP 3A4 Inducer and substrate	Fosamprenavir	No data of interactin between fosamprenavir and rifabutin; interaction between amprenavir and rifabutin suggests inhibition of rifabutin metabolism	Decrease rifabutin dose by 50% (to 150 mg/day or 300 mg TIW); if used with ritonavir/fosamprenavir combination, dose reduction to 150 mg every other day or three times weekly
	Itraconazole	Itraconazole conc. decreased by 70%; potential for inhibition of rifabutin metabolism and increased rifabutin conc.	Avoid concomitant use if possible; if the combination is to be used, monitor itraconazole level and adjust dose accordingly; monitor for rifabutin toxicity
	Indinavir	Rifabutin AUC increased 204%; Indinavir AUC decreased 32%	Decrease rifabutin dose to 150 mg/day or 300 mg TIW and increase unboosted indinavir dose to 1000 mg every 8 hours
	Ketoconazole	Possible increase in rifabutin conc. and decrease in ketoconazole conc.	Monitor for rifabutin toxicities and ketoconazole efficacy
	Lopinavir/ritonavir (Kaletra®)	Rifabutin AUC increased 303%; 25-O-des-acetyl rifabutin AUC increased 47.5-fold	Decrease rifabutin dose to 150 mg every other day or three times weekly
	Nelfinavir	Rifabutin AUC increased 207%; insignificant change in nelfinavir conc.	Decrease rifabutin dose to 150 mg/day or 300 mg TIW
	Ritonavir	Rifabutin AUC increased 430%; no change in ritonavir conc.	Decrease rifabutin dose to 150 mg every other day or three times weekly
	Saquinavir	Saquinavir AUC decreased 43%; no change in rifabutin conc.	This combination should be avoided; might consider adding ritonavir to saquinavir or monitor saquinavir conc.
	Voriconazole	Voriconazole AUC decreased 79%; rifabutin AUC increased three-fold	This combination should be avoided
Rifampin	Amprenavir	Amprenavir AUC decreased 82%, Cmin decreased 92%; no change in Rifampin conc.	This combination should be avoided; effect of rifampin on ritonavir and amprenavir has not been studied
Potent CYP3A4 Inducer	Atazanavir	Pharmacokinetic study not available; expect rifampin to decrease atazanavir concentrations substantially (up to 90%), as seen with other protease inhibitors	This combination should be avoided
	Atovaquone	Atovaquone conc. decreased 52%; rifampin conc. increased 37%	This combination should be avoided
	Clarithromycin	Decreased mean clarithromycin conc. 87%	This combination should be avoided; consider switching clarithromycin to azithromycin
	Dapsone	Dapsone half-life decreased from 24 to 11 hr; dapsone conc. decreased 7–10 fold	Monitor for dapsone efficacy; consider alternative therapy
	Delavirdine	Delavirdine AUC decreased 95%; no change in rifampin conc.	This combination should be avoided
	Efavirenz	Efavirenz AUC decreased 22%; no change in rifampin conc.	No dosage adjustment or consider increasing efavirenz dose to 800 mg/day
	Fluconazole	Fluconazole AUC decreased by 23%–56%; no change in rifampin conc.	Might need to increase fluconazole dose
	Fosamprenavir	No study done with fosamprenavir to date; amprenavir AUC decreased 82%; Cmin decreased 92%	This combination should be avoided
	Indinavir	Indinavir AUC decreased 89%; rifampin conc. slightly increased	This combination should be avoided
	Itraconazole	Itraconazole AUC decreased 64%–88%; no change in rifampin conc.	Avoid concomitant use if possible; if the combination is to be used, monitor itraconazole level and adjust dose accordingly; monitor therapeutic response
	Ketoconazole	Ketoconazole levels decreased 50%	Avoid concomitant use if possible; consider alternative antifungal and/or antimycobacterial agent(s)

TABLE 8. (*Continued*) Substantial pharmacokinetic drug-drug interactions for drugs used in the treatment of opportunistic infections*

Drugs	Interacting with	Mechanism/effects	Recommendations
Rifampin (*Continued*)	Lopinavir/ritonavir (Kaletra®)	Lopinavir AUC decreased 75% and Cmin decreased 99%; Rifampin AUC might be increased	This combination should be avoided
Potent CYP3A4 Inducer	Nelfinavir	Nelfinavir AUC decreased 82%; no change in rifampin conc.	This combination should be avoided
	Nevirapine	Nevirapine maximum concentration (Cmax) and AUC decreased by >50%; no change in rifampin conc.	This combination should be avoided
	Ritonavir	Ritonavir AUC decreased 35%; no change in rifampin conc.	Monitor for antiretroviral activity of ritonavir
	Saquinavir	Saquinavir AUC decreased 84%; no change in rifampin conc.	This combination should be avoided; use only in the presence of ritonavir, consider monitoring saquinavir concentration
	Trimetrexate	Might increase trimetrexate metabolism and decrease trimetrexate conc.	Monitor for trimetrexate efficacy
	Voriconazole	Voriconazole AUC decreased 96%	This combination should be avoided
	Zidovudine	Rifampin increased zidovudine glucuronidation, decreasing zidouvdine AUC 47%	Monitor for zidovudine efficacy
Tenofovir	Acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir	Potential for compete active tubular secretion of these drugs	Monitor for toxicities of these drugs and tenofovir
	Atazanavir	Atazanavir Cmin decreased 40%; mechanism unknown	Co-administer with ritonavir at a dose of ritonavir 100 mg daily plus atazanavir 300 mg daily
	Didanosine (buffered and enteric coated preparations)	Increased didanosine AUC by 44%–60%; no change in tenofovir AUC	Reduce didanosine dose (from 400 mg to 250 mg in patients weighing >60 mg); monitor for didanosine-associated toxicities; discontinue didanosine if serious toxicity occurs
Trimetrexate CYP 3A4 substrate	CYP 3A4 Inhibitors (e.g. clarithromycin, delavirdine, fluconazole, itraconazole, ketoconazole, voriconazole, protease inhibitors)	Might increase trimetrexate concentration	Monitor for trimetrexate toxicities
	CYP 3A4 Inducers (e.g. efavirenz, nevirapine, rifabutin, rifampin)	Might decrease trimetrexate concentration	Monitor for trimetrexate efficacy
Valganciclovir	Cidofovir plus Probenecid	Probenecid might decrease ganciclovir renal clearance and increase ganciclovir conc.	Because of the infrequent dosing of probenecid when used with cidofovir, no dosage adjustment is necessary; monitor for dose-related toxicities
	Didanosine buffered formulation	Oral ganciclovir increased didanosine AUC 111%	Monitor for didanosine toxicities; study with valganciclovir and didanosine enteric coated formuation has not been done
Voriconazole	Delavirdine	Potential bi-directional inhibition of metabolism, increasing conc. of both drugs	No formal interaction studies; monitor for toxicities
CYP 2C9, 2C19, and 3A4 Substrate and inhibitor	Efavirenz	Voriconazole Cmax decreased 61%; AUC decreased 77%; efavirenz Cmax increased 38% and AUC increased 44%	This combination should be avoided
	Nevirapine	Potential induction of voriconazole metabolism, decreasing voriconazole conc.	No formal interaction studies; monitor for therapeutic failure of voriconazole
	Protease inhibitors (except indinavir and ritonavir)	Potential bi-directional inhibition of metabolism, increasing conc. of both drugs; Indinavir and voriconazole lead to no substantial interaction	No formal interaction studies except for indinavir and ritonavir; monitor for toxicities
	Rifabutin	Voriconazole AUC decreased 79%; Rifabutin AUC increased three-fold	This combination should be avoided
	Rifampin	Voriconazole AUC decreased 96%	This combination should be avoided
	Ritonavir	Ritonavir, at a dose of 400 mg twice a day, decreased voriconazole Cmax 66% and AUC 82%; effect of lower ritonavir doses (100–400 mg/day) on variconazole pharmacokinetics unknown	Use with ritonavir 400 mg twice a day should be avoided; use with other doses of ritonavir should be done with caution