Table 5: Significant Drug Interactions for Drugs Used to Treat or Prevent Opportunistic Infections (Last updated November 6, 2013; last reviewed November 6, 2013)

There is the potential for significant drug interactions and overlapping toxicities in patients receiving medications for treatment or prevention of opportunistic infections (OIs). These patients often are receiving other medications, including antiretrovirals that interfere with metabolism or elimination of OI medications. In particular, protease inhibitors and non-nucleoside reverse transcriptase inhibitors affect the CYP450 or other transporter systems and may be associated with clinically significant drug interactions. The integrase inhibitor raltegravir is metabolized by UGT1A1 and may be a suitable option when trying to minimize interactions with other drug classes.

Table 5 provides clinicians with information regarding known or suspected drug interactions between drugs commonly used for treatment or prevention of HIV-associated OIs and treatment of HIV infection. Drug interaction information is generally obtained from studies involving healthy adult volunteers. Some pharmacokinetic (PK) data are available from studies involving HIV-infected adults, whereas data in children are extremely limited. New information continues to become available and it is important to carefully review a patient's current medications, including prescription and over-the-counter medications. It is difficult to predict the interaction potential when three or more drugs with similar metabolic pathways are co-administered and there is substantial inter-patient variability in the magnitude of these interactions. When possible, alternative agents with less drug interaction potential or use of therapeutic drug monitoring should be considered.

Table 5 contains only a partial listing of drug interactions for drugs used to treat or prevent OIs. The links below are excellent resources for investigating the potential for drug interactions. These tools include more comprehensive information and provide up-to-date information as new PK data become available.

http://www.hiv-druginteractions.org/

http://tdm.pharm.buffalo.edu/home/di_search/

http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/32/drug-interactions/

http://www.drugs.com/drug_interactions.html

http://hivinsite.ucsf.edu/InSite?page=ar-00-02

http://www.nynjaetc.org/clinical_support.html

http://www.clinicaloptions.com/inPractice.aspx

http://epocrates.com

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Drug Name	Overlapping Toxicities	Recommendation
*** The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions).**		
Acyclovir (Zovirax)	Overlapping Toxicities: • Nephrotoxic drugs	Monitor for toxicities of these drugs.
	Increased Concentrations (Both Drugs) and Overlapping Toxicities: • Antivirals: valacyclovir, valganciclovir, ganciclovir, cidofovir • ARVs: tenofovir	Monitor for toxicities of these drugs.
Albendazole	Increases Albendazole Concentrations: • Anthelmintic drugs: praziquantel	Caution advised.
Amikacin	Overlapping Toxicities: • Anti-tuberculosis drugs (injectable): streptomycin, kanamycin • Nephrotoxic or ototoxic drugs • Antimycobacterial drugs: capreomycin • Antivirals: cidofovir	Caution advised. Avoid combination of amikacin and cidofovir.
Amphotericin B Amphotericin B Lipid Complex (Abelcet) Amphotericin B Liposome (Ambisome)	Overlapping Toxicities: • Bone marrow suppressant drugs: corticosteroids • Nephrotoxic drugs • Neuromuscular blocking drugs	Caution advised.
Atovaquone	Decreases Atovaquone Concentrations: • Antimycobacterial drugs: rifampin, rifabutin • ARVs: lopinavir/ritonavir, atazanavir/ritonavir • Antibiotics: doxycycline	Co-administration of atovaquone and rifampin should be avoided.
Azithromycin	Overlapping Toxicities: • Artemether/lumefantrine, chloroquine, quinine	Caution advised. Increased risk of QT prolongation.
Boceprevir	Please see Adult OI guidelines for information about drug interactions, including warnings about interactions between boceprevir and HIV protease inhibitors.	
Capreomycin	Overlapping Toxicities: • Nephrotoxic or ototoxic drugs • Neuromuscular blocking drugs • Antibacterial drugs: aminoglycosides (parenteral)	Caution advised.
Caspofungin	Decreases Caspofungin Concentrations: • Anticonvulsant drugs: phenytoin • Antimycobacterial drugs: rifampin • ARV drugs: efavirenz, nevirapine	Increase in dose of caspofungin is recommended when co-administered with CYP450 inducers.

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Drug Name	Overlapping Toxicities	Recommendation
*** The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions).**		
Cidofovir	Overlapping Toxicities: • Antibacterial drugs: aminoglycosides • Antiviral drugs: foscarnet • Nephrotoxic drugs	Monitor for toxicities of these drugs.
Ciprofloxacin	Decreases Ciprofloxacin Absorption: • ARV drugs: didanosine • Minerals: ferrous sulfate, zinc • Gastrointestinal drugs: antacids, sucralfate, magnesium-containing laxatives	Give oral ciprofloxacin 2 hours before or 6 hours after drugs that may interfere with absorption.
	Overlapping Toxicities: • Artemether/lumefantrine, clarithromycin, quinine	Caution advised.
Clarithromycin	Increases Clarithromycin Concentrations: • ARV drugs: atazanavir/ritonavir, lopinavir/ritonavir • Antifungals: itraconazole (itraconazole concentrations also increased)	Caution advised. Concern for QTc prolongation. Decrease clarithromycin dose or consider switching to azithromycin, which has less potential for drug interactions.
	Increases Concentration of Other Medications: • ARV drugs: etravirine	Consider alternative agent.
	Decreases Clarithromycin Concentrations: • ARV drugs: efavirenz, etravirine, nevirapine • Antimycobacterial drugs: rifampin, rifabutin (rifabutin concentrations also increased)	Consider switching to azithromycin, which has less potential for drug interaction. For concomitant use of rifabutin and clarithromycin, consider decreasing dose of rifabutin or switching to azithromycin.
Clindamycin	Decreases Clindamycin Antibacterial Efficacy: • Antibacterial drugs: chloramphenicol, erythromycins	Avoid concomitant use.
Cycloserine	Overlapping Toxicities: • Antimycobacterial drugs: ethionamide, isoniazid	Caution advised.
Dapsone	Decreases Dapsone Concentrations: • Antimycobacterial drugs: rifampin	Co-administration should be avoided if possible. Consider alternatives for dapsone or use rifabutin.
	Decreases Dapsone Absorption: • ARV drugs: didanosine suspension • Gastrointestinal drugs: antacids	For co-administration with antacids or didanosine suspension, give dapsone 1 hour before or 4 hours after the other medication.
	Overlapping Toxicities: • Bone marrow suppressant drugs or drugs associated with hemolysis	Caution advised.
Doxycycline	Decreases Doxycycline Concentrations: • Anticonvulsant drugs: phenytoin, carbamazepine • Antimycobacterial drugs: rifampin	Potential for decreased doxycycline efficacy. Monitor for therapeutic failure.

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*** The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions).**		
Erythromycin	Increases Concentrations of Erythromycin and Co-Administered Medication: • Antifungals: itraconazole	Monitor for toxicities of both drugs, potential for QT prolongation.
Ethambutol	Overlapping Toxicities: • Neurotoxic drugs	Caution advised.
Ethionamide	Potential for Increased Toxicity Due to Overlapping Toxicity: • Neurotoxic drugs • Antimycobacterial drugs: cycloserine, isoniazid	Caution advised.
Fluconazole	Decreases Fluconazole Levels: • Anticonvulsant drugs: phenytoin • Antimycobacterial drugs: rifampin • ARV drugs: rilpivirine	Monitor for efficacy. May need to increase fluconazole dose.
	Increases Concomitant Drug Concentrations: • ARV drugs: saquinavir, tipranavir, nevirapine, and etravirine	May need to decrease dose of saquinavir. Avoid tipranivir with high doses of fluconazole (maximum fluconazole dose in adults: 200 mg). Caution advised with etravirine.
	• Antimycobacterial drugs: rifabutin	May need to decrease dose of rifabutin.
	• Statins: simvastatin, lovastatin, atorvastatin	Do not co-administer with simvastatin or lovastatin. Avoid use of atorvastatin if possible. Alternative statins such as fluvastatin, rosuvastatin, pravastatin are preferred or discontinue statin during antifungal therapy.
Flucytosine	Increases Flucytosine Concentrations: • Nephrotoxic drugs	Caution advised.
Foscarnet	Overlapping Toxicities: • Antiviral drugs: cidofovir • Anti-pneumocystis drugs: pentamidine • Nephrotoxic drugs	Monitor for toxicities of these drugs.
Ganciclovir	Increases Ganciclovir Concentrations : • ARV drugs: tenofovir (concentrations also increased)	Monitor for toxicities of these drugs.
	Increases Concomitant Drug Concentrations: • ARV drugs: didanosine, tenofovir	Caution advised.
	Overlapping Toxicities: • Antibacterial drugs: imipenem-cilastatin • ARV drugs: zidovudine • Bone marrow suppressant drugs • Nephrotoxic drugs	Caution advised. Increased risk of seizures with imipenem-cilastatin.

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Drug Name	Overlapping Toxicities	Recommendation
*** The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions).**		
Interferon-Alfa	Overlapping Toxicities: • ARV drugs: zidovudine, lamivudine • Bone marrow suppressant drugs	Co-administration of zidovudine and lamivudine should be avoided if possible. Caution advised with other bone marrow suppressant drugs.
Isoniazid	Decreases Isoniazid Concentrations: • Corticosteroids: glucocorticoids (e.g., prednisolone)	Use with caution.
	Decreases Isoniazid Absorption: • Gastrointestinal drugs: antacids	Caution advised.
	Increases Concomitant Drug Concentrations: • Diazepam	Caution advised.
	Decreases Concomitant Drug Concentrations: • Antifungal drugs: ketoconazole, itraconazole	Co-administration should be avoided, if possible.
	Overlapping Toxicities: • Antimycobacterial drugs: rifampin, cycloserine, ethionamide • Hepatotoxic drugs • Neurotoxic drugs	Caution advised.
Itraconazole	Increases Itraconazole Concentration: • Antibacterial: clarithromycin, erythromycin, ciprofloxacin • ARVs: protease inhibitors	Monitor for toxicities. Monitor itraconazole concentration. Consider azithromycin instead of other macrolides. High doses of itraconazole are not recommended with PIs.
	Increases Concomitant Drug Concentrations: • ARV drugs: etravirine, maraviroc, protease inhibitors	Caution advised. Monitor for toxicities. Decrease adult maraviroc dose to 150 mg twice daily.
	• Statins: lovastatin, simvastatin, atorvastatin	Do not co-administer with simvastatin or lovastatin. Avoid use of atorvastatin if possible. Alternative statins such as fluvastatin, rosuvastatin, pravastatin are preferred or discontinue statin during antifungal therapy.
	• Antibacterial: clarithromycin, erythromycin	Consider switching to azithromycin, which has less potential for drug interaction.
	• Sedatives/hypnotics: midazolam, alprazolam, diazepam	Co-administration of midazolam and alprazolam should be avoided. Co-administration of diazepam should be avoided, if possible.
	• Cardiac: quinidine	Co-administration of quinidine should be avoided. QT prolongation.
	Decreases Itraconazole Concentrations: • ARV drugs: efavirenz, etravirine, nevirapine, rilpivirine	Monitor itraconazole concentration. Co-administration of efavirenz should be avoided if possible.
	• Anticonvulsant drugs: carbamazepine, (fos)phenytoin	Monitor itraconazole concentration.

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Drug Name	Overlapping Toxicities	Recommendation
*** The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions).**		
Itraconazole, continued	• Antimycobacterial drugs: rifampin, rifabutin, rifapentine, isoniazid	Co-administration with rifampin should be avoided. Co-administration with rifabutin should be avoided, if possible. Monitor for toxicities. Monitor itraconazole concentration.
	Decreases Itraconazole Absorption: • ARV drugs: didanosine • Gastrointestinal drugs: antacids, anticholinergics/antispasmodics, histamine H_2-receptor antagonists, omeprazole, sucralfate	Monitor itraconazole concentration.
Lumefantrine	Increases Concomitant Drug Levels: • ARV drugs: nevirapine	Monitor for nevirapine toxicity.
	Overlapping Toxicities: • ARV drugs: protease inhibitors • Antibacterial drugs: macrolides, fluoroquinolones • Antifungal drugs: fluconazole, voriconazole • Antimalarial drugs: quinine, quinidine • Psychotropic drugs: quetiapine, tricyclic antidepressants	Co-administration with fluconazole or voriconazole should be avoided. For all other drugs, co-administration should be avoided, if possible; monitor for toxicities (QT prolongation).
Mefloquine	Decreases Mefloquine Concentrations: • Antimalarial drugs: quinine • Antimycobacterial: rifampin	Monitor for decreased mefloquine efficacy. Co-administration of rifampin should be avoided, if possible; use rifabutin instead.
	Decreases Concomitant Drug Concentrations: • ARV drugs: ritonavir, possibly other protease inhibitors	Monitor for virologic failure of protease inhibitor-containing ART regimen.
	Overlapping Toxicities: • Anti-malarial drugs: quinine • Other drugs that can cause prolonged QT	Avoid co-administration, if possible. Monitor for toxicities (EKG changes, cardiac arrest; also seizures with quinine). If co-administered with quinine, give mefloquine at least 12 hours after last dose of quinine.
Nitazoxanide	Increases Concomitant Drug Concentrations: • Phenytoin	Potential for interaction with other medications that are highly protein bound. Use with caution as interaction will increase concentrations of concomitant medication.
Paromomycin	Overlapping Toxicities: • Neuromuscular blocking drugs	Use with caution.

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Drug Name	Overlapping Toxicities	Recommendation
*** The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions).**		
Pentamidine	Overlapping Toxicities: • Antiviral drugs: foscarnet	Co-administration should be avoided, if possible. Monitor for toxicities (hypocalcaemia, QT prolongation).
	• ARV drugs: protease inhibitors, didanosine	Co-administration should be avoided, if possible. Monitor for toxicities (QT prolongation with protease inhibitors; pancreatitis for didanosine).
	• Bone marrow suppressant drugs	Monitor for toxicities.
	• Nephrotoxic drugs	Monitor for toxicities.
	• Other drugs that can cause prolonged QT	Monitor for toxicities. Avoid co-administration, if possible.
Posaconazole	Decreases Posaconazole Drug Concentrations: • ARV drugs: efavirenz, fosamprenavir, rilpivirine	Co-administration of fosamprenavir should be avoided. Co-administration of efavirenz should be avoided, if possible. If co-administered, monitor posaconazole concentrations and adjust dose accordingly.
	• Anticonvulsant drugs: phenytoin	Co-administration should be avoided, if possible. If co-administered, monitor posaconazole concentrations and adjust dose accordingly.
	• Antimycobacterial drugs: rifabutin, rifampin	Co-administration should be avoided, if possible. If co-administered, monitor posaconazole concentrations and adjust dose accordingly.
	Increases Concomitant Drug Concentrations: • ARV drugs: atazanavir, saquinavir, lopinavir, etravirine, and ritonavir	Co-administration should be avoided, if possible. Monitor for toxicities. Consider monitoring concentrations and adjust dose as necessary.
	• Antibacterial drugs: erythromycin, clarithromycin	Co-administration should be avoided.
	• Anticonvulsant drugs: phenytoin	Co-administration should be avoided.
	• Sedatives/hypnotics: midazolam, alprazolam, diazepam	Co-administration should be avoided, if possible. Monitor for toxicities.
	• Antimycobacterial drugs: rifabutin	Co-administration should be avoided.
	• Statins: simvastatin, lovastatin, atorvastatin	Do not co-administer with simvastatin or lovastatin. Avoid use of atorvastatin if possible. Alternative statins such as fluvastatin, rosuvastatin, pravastatin are preferred or discontinue statin during antifungal therapy.
	• Antimalarials: Quinidine, quinine, mefloquine, lumefantrine, halofantrine	Co-administration should be avoided.
	Decreases Concomitant Drug Concentrations: • ARV drugs: fosamprenavir	Co-administration should be avoided.
	• Other drugs that can cause prolonged QT	Use with caution. Monitor for toxicities.

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Drug Name	Overlapping Toxicities	Recommendation
*** The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions).**		
Proguanil	Decreases Proguanil Concentrations: • Atazanavir/ritonavir, lopinavir/ritonavir, efavirenz	Use with caution.
Pyrazinamide	Overlapping Toxicities: • Antimycobacterial drugs: rifampin, ethionamide • Hepatotoxic drugs	Use with caution. Monitor for hepatotoxicity.
Quinidine	Increases Quinidine Concentrations: • Protease inhibitors	Co-administration of PIs should be avoided. Increased risk of arrhythmia. Co-administration may be necessary in presence of life-threatening, severe malaria and in the absence of other therapy, while artesunate is obtained from the CDC.
	• Itraconazole, posaconazole, voriconazole	Co-administration should be avoided. Increased risk of arrhythmia.
	Decreases Quinidine Concentrations: • Etravirine	Use with caution. Monitor quinidine levels.
	Increases Concomitant Drug Concentrations: • Tricyclic antidepressants	Co-administration should be avoided, if possible. Monitor for toxicities.
	Overlapping Toxicities: • Other drugs that can prolong QT interval	Co-administration should be avoided, if possible. Monitor for toxicities (QT prolongation).
Ribavirin	Increases Concentrations Of Concomitant Drug: • ARV drugs: didanosine	Co-administration should be avoided. Potential for increased risk of pancreatitis and mitochondrial toxicity.
	Decreases Concentrations of Concomitant Drug: • Zidovudine, stavudine	Co-administration should be avoided, if possible.
	Overlapping Toxicities: • Zidovudine, all NRTIs	Co-administration should be avoided, if possible. Monitor for toxicities (anemia for zidovudine; lactic acidosis for all NRTIs).
Rifabutin	Increases Rifabutin Concentrations: • HIV protease inhibitors	Use with caution. Monitor for rifabutin toxicity. Reduce rifabutin dose if co-administered with PIs.
	• Fluconazole	Use with caution. Monitor for rifabutin toxicity. Consider rifabutin dose reduction.
	• Voriconazole, itraconazole, posaconazole	Co-administration should be avoided, if possible. If co-administered, consider TDM and monitor for rifabutin toxicities (and azole clinical efficacy).
	• Clarithromycin	Co-administration should be avoided, if possible. Monitor for rifabutin toxicity. Consider rifabutin dose reduction or using azithromycin instead.
	Increases Concomitant Drug Concentrations: • Didanosine	Use with caution. Monitor for didanosine toxicity.

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*** The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions).**		
Rifabutin, continued	Decreases Rifabutin Concentrations: • Efavirenz, etravirine	Use with caution. Higher rifabutin dose required when efavirenz co-administered. Consider TDM.
	Decreases Concomitant Drug Concentrations: • ARV drugs: rilpivirine	Co-administration should be avoided.
	• ARV drugs: saquinavir, etravirine, maraviroc	Co-administration should be avoided, if possible.
	• Antibacterial drugs: dapsone, atovaquone	Use with caution. Monitor for dapsone treatment failure.
	• Antifungal drugs: azoles (except for fluconazole)	Co-administration should be avoided, if possible. If co-administered, consider TDM and monitor for rifabutin toxicities (and azole clinical efficacy).
	• Contraceptives: oral	Oral contraceptives less effective. Additional non-hormonal contraceptive or alternative recommended.
Rifampin	Decreases Concomitant Drug Concentrations: • Contraceptives: oral	Oral contraceptives less effective. Additional non-hormonal contraceptive or alternative recommended.
	• ARV drugs: PIs ± ritonavir, nevirapine, raltegravir, rilpivirine	Significantly decreases PI exposure; co-administration should be avoided. Nevirapine: use only if other options not available and close virologic and immunologic monitoring can be done; consider efavirenz instead. Raltegravir dose increase may be required. Rilpivirine co-administration should be avoided.
	• Antimicrobial: atovaquone, dapsone, clarithromycin, doxycycline	Co-administration of atovaquone and rifampin should be avoided. Consider switching clarithromycin to azithromycin, which has less potential for drug interaction. Dapsone and Doxycycline efficacy may be reduced.
	• Antifungal drugs: azoles, caspofungin	Increase in dose of caspofungin is recommended when co-administered with CYP450 inducers. Azoles: Monitor for efficacy. May need to increase antifungal dose
	• Other: corticosteroids, methadone	Caution advised with corticosteroids (decreased efficacy). Methadone: Monitor for efficacy and/or opiate withdrawal symptoms with methadone.
	Overlapping Toxicities: • Bone marrow suppressant drugs • Hepatotoxic drugs	Monitor for toxicities of these drugs.
Streptomycin	Potential for Increased Toxicity Due to Overlapping Toxicity: • Nephrotoxic drugs • Neuromuscular blocking drugs	Monitor for toxicities of these drugs.

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Drug Name	Overlapping Toxicities	Recommendation
*** The drug interactions included in this table were selected on the basis of their potential clinical significance and are not inclusive of all potential drug interactions (see drug label and the drug interaction websites listed for complete information on drug interactions).**		
Telaprevir	Please see Adult OI guidelines for information about drug interactions, including warnings about interactions between telaprevir and HIV protease inhibitors. Caution advised.	
Trimethoprim-Sulfamethoxazole	Overlapping Toxicities: • Folate antagonists • Bone marrow suppressant drugs	Monitor for toxicities of these drugs.
Valacyclovir	Potential For Increased Concentrations (of Both Drugs) and Overlapping Toxicity: • Antivirals: acyclovir, valganciclovir, ganciclovir, cidofovir • ARVs: tenofovir	Monitor for toxicities of these drugs.
Valganciclovir	Potential for Increased Concentrations (of Both Drugs) and Overlapping Toxicity: • Antivirals: valacyclovir, acyclovir, ganciclovir, cidofovir • ARVs: tenofovir	Monitor for toxicities of these drugs.
Voriconazole	Decreases Voriconazole Concentrations: • Anticonvulsant drugs: carbamazepine, long-acting barbiturates	Caution advised.
	• Antimycobacterial drugs: rifabutin, rifampin	Rifabutin and Rifampin co-administration should be avoided.
	• ARV drugs: efavirenz, nevirapine, PIs boosted with ritonavir	Standard doses of efavirenz and voriconazole should not be used; voriconazole dose may need to be increased and efavirenz dose decreased, or use alternative antifungal agent. Potential for increased PI concentrations and decreased voriconazole concentrations; consider monitoring voriconazole concentrations and adjust dose accordingly; monitor for PI-associated toxicities or consider using an alternative antifungal agent.
	Increases Voriconazole Concentrations: • ARV drugs: etravirine	Monitor voriconazole concentrations to reduce toxicity.
	Increases Concomitant Drug Concentrations: • Antimycobacterial drugs: rifabutin	Caution advised.
	• ARV drugs: protease inhibitors boosted with ritonavir, efavirenz, etravirine	Caution advised.
	• Statins: simvastatin, lovastatin, atorvastatin	Statins: Do not co-administer with simvastatin or lovastatin. Avoid use of atorvastatin if possible. Alternative statins such as fluvastatin, rosuvastatin, pravastatin are preferred or discontinue statin during antifungal therapy.
	• Sedatives/hypnotics: midazolam, alprazolam, triazolam	Co-administration should be avoided if possible. Monitor for toxicities.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; CDC = Centers for Disease Control and Prevention; EKG = electrocardiogram; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; OI = opportunistic infection; PI = protease inhibitors; PK = pharmacokinetic; TDM = therapeutic drug monitoring