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Common Drug Interactions Encountered in Treating Transplant-Related Infection

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The treatment of patients with transplant-related infections requires close attention to the host in order to ensure adequate and safe dosing of anti-infective medications. Solid organ transplant recipients are at risk for synergistic toxicities due to drug–drug interactions between anti-infective agents and immunosuppressive medications. These toxicities relate to consequences of high exposures to the immunosuppressive and/or the anti-infective medication. While perhaps less frequent, the risk of inadequate anti-infective drug exposure and resulting treatment failure due to drug–drug interactions must also be avoided. This chapter presents a summary of the clinically significant drug–drug interactions encountered in providing anti-infective chemotherapy to solid organ transplant recipients.

Medications used for immunosuppression after organ transplantation can be split into seven categories (Table 4-1): polyclonal antibodies, monoclonal antibodies, calcineurin inhibitors, antimetabolites, mammalian target of rapamycin (mTOR) inhibitors, corticosteroids, and selective T-cell costimulation blockers. The reader is referred to Chap. 3 for more detailed information regarding the mechanism of action of these commonly used immunosuppressive agents. The risk of drug interactions is high, particularly within the calcineurin inhibitor and mTOR inhibitor drug classes.

Cyclosporine (Neoral, Sandimmune, Novartis Pharmaceuticals) and tacrolimus (Prograf, Astagraf XL, Astellas Pharmaceuticals) are calcineurin inhibitors. They suppress the immune system by blocking IL-2 signaling between immune cells. Major toxicities include electrolyte disturbances (i.e., hypophosphatemia, hypomagnesemia, hyperkalemia), hypertension, hyperlipidemia, hyperglycemia, nephrotoxicity, neurotoxicity, and others [1, 2]. Doses are adjusted to obtain target whole blood cyclosporine or tacrolimus levels and the target range is patient-specific.

Sirolimus (Rapamune, Pfizer Inc.) and everolimus (Zortress, Novartis Pharmaceuticals) are mTOR inhibitors whose actions inhibit T-cell activation and proliferation. Major toxicities include impaired wound healing, hypertriglyceridemia, hyperlipidemia, oral ulcers, proteinuria, and noninfectious pneumonitis [3–6]. Sirolimus and everolimus doses are adjusted to obtain target whole blood trough concentrations, and the target range is patient-specific. Sirolimus has a long half-life and it will take 1–2 weeks to reach steady state after initiating therapy and/or after dose changes.

Cyclosporine, tacrolimus, sirolimus, and everolimus are substrates for both cytochrome P-450 3A4 (CYP3A4) and P-glycoprotein (P-gp). Drugs and substances that induce CYP3A4 and/or P-gp may decrease cyclosporine/tacrolimus/sirolimus/everolimus concentrations, whereas inhibitors of CYP3A4 and/or P-gp may increase cyclosporine/tacrolimus/sirolimus/everolimus concentrations. Cyclosporine also inhibits CYP3A4 and P-gp and may have additional unique drug interactions not present with tacrolimus, sirolimus, and everolimus.

Azathioprine (Imuran; Prometheus Laboratories) is an antimetabolite. Major toxicities include bone marrow suppression manifesting as leukopenia, thrombocytopenia, and anemia. Standard, weight-based dosing is used for azathioprine; serum drug concentrations are not utilized [7].

Mycophenolate mofetil (MMF, CellCept; Genentech) and mycophenolic acid (MPA, Myfortic; Novartis Pharmaceuticals) are also antimetabolites, but, compared with azathioprine, their mechanism of action is more targeted to the white blood cell lines. Major toxicities include leukopenia and gastrointestinal adverse effects, most notably diarrhea [8]. Although these drugs are generally used at standard doses, therapeutic drug monitoring may be useful for MMF.

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MMF is a prodrug that, after absorption, is quickly hydrolyzed to MPA. Myfortic is an enteric coated formulation of MPA, which is the active moiety of both these drugs. The major metabolite of MPA, an MPA glucuronide known as MPAG, is excreted into urine and bile. Once in the GI tract, MPAG is converted back into MPA and reabsorbed, resulting in enterohepatic recirculation.

MMF and MPA are believed to have similar drug interactions. Indeed, most MPA drug interactions are derived from the MMF literature. The clinical impact may not be exactly the same, however, because each of these medications has a unique pharmacokinetic profile. In addition to the interactions listed in Table 4-2, drugs that alter the GI flora may disrupt enterohepatic recirculation of MPA. This is because natural GI flora is responsible for conversion of MPAG to MPA [75].

TABLE 4-1. Immunosuppressive agents [7]

Class	Generic name	Brand name
Calcineurin inhibitors	Cyclosporine	Neoral; Sandimmune
	Tacrolimus	Prograf; Astagraf XL
Antimetabolites	Azathioprine	Imuran
	Mycophenolate mofetil	CellCept
	Mycophenolic acid	Myfortic
Corticosteroids	Prednisone	Deltasone
mTOR inhibitors	Sirolimus	Rapamune
	Everolimus	Zortress
Polyclonal antibodies	Antithymocyte globulin, rabbit	Thymoglobulin
Monoclonal antibodies	Basiliximab (anti-CD25)	Simulect
	Alemtuzumab (anti-CD52)	Campath-1H
Selective T-cell costimulation blocker	Belatacept	Nulojix

For more information, also see Chap. 3.
Abbreviation: *mTOR* mammalian target of rapamycin.

There is scant evidence suggesting that corticosteroids may have clinically relevant drug interactions with other immunosuppressive agents [76]. Corticosteroids induce the CYP3A4 and P-gp pathways to varying degrees; cyclosporine, tacrolimus, sirolimus, and everolimus rely on these pathways for metabolism. Corticosteroids also induce uridine diphosphate glucuronosyltransferase enzymes and multidrug resistance-associated protein 2; the mycophenolate products rely on these pathways for metabolism. When possible, therapeutic drug monitoring can be used to ensure appropriate immunosuppressive exposure while initiating or tapering corticosteroids [7].

Relevant drug interactions have not been noted for the polyclonal/monoclonal antibodies or selective T-cell costimulation blockers. These drugs do, however, pose the risk of pharmacodynamic interactions and additive toxicities.

Since our last update, several new anti-infective medications have been approved for marketing. These include the antibacterial drugs tedizolid, ceftaroline, dalbavancin, oritavancin, ceftolozane–tazobactam, fidaxomicin, and ceftazidime–avibactam. New antiviral agents include antihepaciviral protease inhibitors (telaprevir, boceprevir, simeprevir), polymerase inhibitors, and NS5A inhibitors as well as antiretroviral integrase inhibitors (raltegravir, elvitegravir, dolutegravir). The new azole antifungal agent isavuconazole was also introduced and is marketed as the prodrug isavuconazonium sulfate. New immunosuppressant agents include everolimus and belatacept. The tables highlight only drugs with potential interactions in transplant recipients. Table 4-1 lists the immunosuppressive agents according to their class; Table 4-2 shows common immunosuppressant interactions; and Table 4-3 presents common interactions between anti-infective and immunosuppressant drugs.

TABLE 4-2. Common immunosuppressant drug interactions

Immunosuppressant	Interacts with	Interaction	Clinical effect	Management
Azathioprine (AZA; Imuran)	Allopurinol [9, 10]	AZA is metabolized to 6-MP (active); 6-MP is inactivated by xanthine oxidase (XO); allopurinol inhibits XO	Significant increase in 6-MP exposure; AZA toxicity (i.e., bone marrow suppression)	Reduce AZA dose; will require 66–75 % AZA dose reduction when adding allopurinol
	Aminosalicylates: mesalamine, olsalazine, sulfasalazine [11, 12]	AZA is metabolized to 6-MP (active); 6-MP is inactivated by TPMT; aminosalicylates may inhibit TPMT	Higher risk of bone marrow suppression	Monitor CBC regularly with concomitant use
	Infliximab [13]	Infliximab reduces AZA clearance	Leukopenia	Monitor CBC regularly with concomitant use
	Warfarin [14]	Unknown	Dose-dependent inhibition of warfarin effect	Titrate warfarin; will require ~2.5-fold higher warfarin when adding AZA
	*Cytochrome P-450 3A4 (CYP3A4) and P-glycoprotein drug interactions also apply			

(continued)

TABLE 4-2. (continued)

Immunosuppressant	Interacts with	Interaction	Clinical effect	Management
Cyclosporine (CSA; Neoral, Sandimmune)	Everolimus [15, 16]	Everolimus is a substrate of CYP3A4 and P-gp; CSA inhibits CYP3A4 and P-gp	Concomitant administration of cyclosporine (Neoral) increases EVR AUC and C_{max} by 168% and 82%, respectively	EVR dose adjustment may be needed upon initiation or discontinuation of cyclosporine Titrate EVR dose; utilize whole blood trough concentrations
	Micafungin [17]	Micafungin is a mild inhibitor of CYP3A4 in vitro; CSA is a CYP3A4 substrate	Concomitant use results in slightly increased CSA exposure	Titrate CSA; utilize whole blood CSA concentrations
	Mycophenolate mofetil [18, 19]	CSA inhibits enterohepatic recirculation of MPAG	30–50% reduction in the MPA $AUC_{0-12\,h}$	Note the alteration in MPA exposure when changing concomitant immunosuppression; consider MMF dose adjustments
	Sirolimus [20–22]	Sirolimus is a substrate of CYP3A4 and P-gp; CSA inhibits CYP3A4 and P-gp	Simultaneous administration increases SIR C_{max} and AUC by 116% and 230%, respectively	Stagger administration by at least 4 h; note that staggered administration minimizes but does not ameliorate the interaction
			Administering SIR 4 h after CSA increases SIR C_{max} and AUC by 37% and 80%, respectively	Titrate SIR; utilize whole blood trough SIR concentrations
	HMG-CoA reductase inhibitors "statins" [23–26]: rosuvastatin, simvastatin > atorvastatin, lovastatin, fluvastatin > pravastatin	Competition for metabolism by CYP3A4; altered statin transport in the liver	Concomitant use results in increased statin exposure; appears more potent with CSA than TAC	Use lower statin doses (i.e., 50% reduced); watch for myopathies and other statin side effects Use with simvastatin and atorvastatin not recommended
	*Cytochrome P-450 3A4 (CYP3A4) and P-glycoprotein drug interactions also apply			
Everolimus (EVR; Zortress)	Cyclosporine [15, 16]	Everolimus is a substrate of CYP3A4 and P-gp; CSA inhibits CYP3A4 and P-gp	Concomitant administration of cyclosporine (Neoral) increases EVR AUC and C_{max} by 168% and 82%, respectively	EVR dose adjustment may be needed upon initiation or discontinuation of cyclosporine Titrate EVR dose; utilize whole blood trough concentrations
	Octreotide [15]	Unknown	Coadministration of EVR with depot octreotide increased C_{min} by 50%	Note altered octreotide exposure with EVR
Mycophenolate mofetil (MMF; CellCept)	Acyclovir, ganciclovir [27]	The antiviral and MPAG compete for renal tubular secretion; particularly in renal impairment	Risk for increased acyclovir, ganciclovir, and MPAG concentrations	Use combination with caution in renal insufficiency; monitor CBC
	Antacids (i.e., Mg, Al) [28]	Impaired absorption of MMF/MPA	25–33% reduction in MPA C_{max} and 17–37% reduction in the MPA $AUC_{0-24\,h}$	Stagger administration by 2–4 h
	Bile acid sequestrants: cholestyramine, colesevelam, colestipol [27, 29]	Drugs that bind bile acids interrupt enterohepatic recirculation	40% reduction in the MPA $AUC_{0-24\,h}$	Avoid concomitant use
	Oral contraceptives [27]	Unknown	Mean levonorgestrel AUC was decreased by 15%	Consider additional method of birth control

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TABLE 4-2. (continued)

Immunosuppressant	Interacts with	Interaction	Clinical effect	Management
	Cyclosporine [18, 19]	CSA inhibits enterohepatic recirculation of MPAG	30–50 % reduction in the MPA $AUC_{0-12\,h}$	Note the alteration in MPA exposure when changing concomitant immunosuppression; consider MMF dose adjustments
	Ganciclovir	See acyclovir		
	Nevirapine [30]	Competition for and/or altered enterohepatic recycling	Slight but significant reduction in nevirapine exposure; unknown effect on MPA	No recommendations have been made
	Proton pump inhibitors [27, 31]	Decreased solubility of MPA at increased gastric pH	MPA C_{max} reduced by 30–70 %, AUC reduced by 25–35 %	Clinical significance unknown Use with caution
	Rifampin [32]	Unknown	Major reduction in MPA $AUC_{0-12\,h}$	Consider MPA drug monitoring while on rifampin
	Sevelamer [33]	Impaired absorption of MMF/MPA	30 % and 25 % reduction in MPA C_{max} and AUC, respectively	Stagger administration by 2 h
Mycophenolic acid (MPA; Myfortic)	Acyclovir, ganciclovir [34]	The antiviral and MPAG compete for renal tubular secretion; particularly in renal impairment	Risk for increased acyclovir, ganciclovir, and MPAG concentrations	Use combination with caution in renal insufficiency; monitor CBC
	Antacids (i.e., Al, Mg) [34]	Antacids decrease MPA absorption	25 % and 37 % reduction in MPA C_{max} and AUC, respectively	Avoid concomitant administration
	Bile acid sequestrants: cholestyramine, colesevelam, colestipol [34]	Drugs that bind bile acids interrupt enterohepatic recirculation	Reduced MPA exposure	Avoid concomitant administration
	Oral contraceptives [34]	Unknown; this interaction is assumed from the MMF experience	Mean levonorgestrel AUC was decreased by 15 %	Consider additional method of birth control
	Cyclosporine [35]	CSA inhibits enterohepatic recirculation of MPAG	20–30 % decrease in the bioavailability and a significant reduction in MPA $AUC_{0-24\,h}$	MPA dose requirements may be higher when used with CSA
	Ganciclovir	See acyclovir		
	*Cytochrome P-450 3A4 (CYP3A4) and P-glycoprotein drug interactions also apply			
Sirolimus (SIR; Rapamune)	Cyclosporine [20–22]	Sirolimus is a substrate of CYP3A4 and P-gp; CSA inhibits CYP3A4 and P-gp	Simultaneous administration increases SIR C_{max} and AUC by 116 % and 230 %, respectively	Stagger administration by at least 4 h; note that staggered administration minimizes but does not ameliorate the interaction
			Administering SIR 4 h after CSA increases SIR C_{max} and AUC by 37 % and 80 %, respectively	Titrate SIR; utilize whole blood trough SIR concentrations
	Micafungin [36]	Unknown	SIR AUC is increased by 21 %; no effect on SIR C_{max}	Consider therapeutic alternatives or titrate SIR doses per whole blood trough SIR concentrations
	*Cytochrome P-450 3A4 and P-glycoprotein drug interactions also apply			

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TABLE 4-2. (continued)

Immunosuppressant	Interacts with	Interaction	Clinical effect	Management
Tacrolimus (TAC; Prograf, Astagraf XL)	HMG-CoA reductase inhibitors "statins": simvastatin, atorvastatin, lovastatin, fluvastatin, pravastatin, rosuvastatin [23, 26]	Competition for metabolism by CYP3A4; altered statin transport in the liver	Concomitant use results in increased statin exposure; appears more potent with CSA than TAC	Use lower statin doses (i.e., 50% reduced); watch for myopathies and other statin side effects
Cytochrome P-450 3A4 (CYP3A4) and P-glycoprotein (P-gp) drug interactions	Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin [15, 20, 37, 38]	Induction of CYP3A4-mediated CSA/TAC/SIR/EVR metabolism	Decrease in plasma CSA/TAC/SIR/EVR concentrations	Titrate CSA/TAC/SIR/EVR dose; utilize CSA/TAC/SIR/EVR whole blood concentrations Consider therapeutic alternatives (i.e., valproic acid, lamotrigine, gabapentin)
	Rifampin [15, 20, 39, 40]			Titrate CSA/TAC/SIR/EVR dose; utilize CSA/TAC/SIR/EVR whole blood concentrations Consider rifabutin if appropriate [41]
	St. John's wort [42, 43]		Unpredictable and varying decrease in CSA/TAC/SIR/EVR concentrations	Avoid concomitant use
	Amiodarone [44] Danazol [45] Nefazodone [46]	Inhibition of CYP3A4-mediated CSA/TAC/SIR/EVR metabolism	Increase in CSA/TAC/SIR/EVR concentrations	Titrate CSA/TAC/SIR/EVR dose; utilize CSA/TAC/SIR/EVR whole blood concentrations
	Grapefruit juice [47]		Unpredictable and varying increase in CSA/TAC/SIR/EVR concentrations	Avoid concomitant use
	Macrolide antibiotics: clarithromycin [48–50], erythromycin [51–53], telithromycin		Significant increase in CSA/TAC/SIR/EVR concentrations	Avoid concomitant use whenever possible; consider azithromycin [54] If coadministration is necessary, empirically reduce CSA/TAC/SIR/EVR doses, monitor CSA/TAC/SIR/EVR whole blood concentrations; titrate CSA/TAC/SIR/EVR dose
	Nondihydropyridine calcium channel blockers: diltiazem [55–57] > verapamil [15, 20, 57]		Increase in CSA/TAC/SIR/EVR concentrations; appears to be more potent with diltiazem versus verapamil	Titrate CSA/TAC/SIR/EVR dose; utilize CSA/TAC/SIR/EVR whole blood concentrations
	Anti-HIV protease inhibitors [58]: amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir [59, 60], nelfinavir, ritonavir [59, 60], saquinavir Anti-HCV protease inhibitors [61]: boceprevir, telaprevir		Significant increase in CSA/TAC/SIR/EVR concentrations	When initiating CSA/TAC/SIR/EVR, use low doses and utilize whole blood concentrations to determine the dosing interval; may need to utilize liquid formulations to achieve small oral doses Titrate CSA/TAC/SIR/EVR dose and/or interval; utilize CSA/TAC/SIR/EVR whole blood concentrations

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TABLE 4-2. (continued)

Immunosuppressant	Interacts with	Interaction	Clinical effect	Management
Azole antifungals: itraconazole [62, 63], posaconazole [64, 65], voriconazole [51, 66], isavuconazole [67] > fluconazole [68, 69], ketoconazole [20] > clotrimazole [70, 71]			For ketoconazole, fluconazole, and clotrimazole: titrate CSA/TAC/SIR/EVR dose and/or interval; utilize CSA/TAC/SIR/EVR whole blood concentrations	
			For voriconazole, posaconazole, and itraconazole: empirically reduce CSA/TAC/SIR/EVR doses, monitor CSA/TAC/SIR/EVR whole blood concentrations; titrate CSA/TAC/SIR/EVR dose	
			For voriconazole, ketoconazole, and itraconazole: note that concomitant use with EVR is not recommended [15]	
			For voriconazole and posaconazole: note that concomitant use with SIR is contraindicated [72, 73] but safe coadministration has been reported [64, 74] if SIR doses are cut by at least 50 % before initiating voriconazole or posaconazole; titrate per SIR whole blood trough concentrations	
			Clotrimazole troches can more than double TAC concentrations due to inhibition of intestinal CYP3A4 and P-gp	

Table 4-3. Common interactions between anti-infective agents and immunosuppressive agents

Anti-infective category	Anti-infective agent/class	Immunosuppressive agent or group of agents	Interaction	Clinical effect	Management
Antifungal	Polyene antifungal: amphotericin B formulations	CSA/TAC/SIR/EVR	Additive nephrotoxicity	Increases risk of kidney injury	Monitor CSA/TAC/SIR/EVR concentration and kidney function
Antifungal	Azole antifungals: itraconazole [62, 63], posaconazole [64, 65], voriconazole [51, 66], isavuconazole [67] > fluconazole [68, 69], ketoconazole [20] > clotrimazole [70, 71]	CSA/TAC/SIR/EVR	Inhibition of CYP3A4	Increases CSA, TAC, SIR, and EVR levels in varying amounts	For ketoconazole, fluconazole, and clotrimazole: titrate CSA/TAC/SIR/EVR dose and/or interval; utilize CSA/TAC/SIR/EVR whole blood concentrations For voriconazole, posaconazole, and itraconazole: empirically reduce CSA/TAC/SIR/EVR doses, monitor CSA/TAC/SIR/EVR whole blood concentrations; titrate CSA/TAC/SIR/EVR dose For voriconazole, ketoconazole, and itraconazole: note that concomitant use with EVR is not recommended [15] For voriconazole and posaconazole: note that concomitant use with SIR is contraindicated [72, 73] but safe coadministration has been reported [64, 74] if SIR doses are cut by at least 50 % before initiating voriconazole or posaconazole; titrate per SIR whole blood trough concentration Clotrimazole troches can more than double TAC concentrations due to inhibition of intestinal CYP3A4 and P-gp
		TAC	Additive QTc prolongation	Increases risk of torsade de pointes	Monitor electrocardiogram for QTc prolongation
Antifungal	Anidulafungin/echinocandin	CSA	No significant interaction		
Antifungal	Caspofungin/echinocandin [77–80]	CSA	increase LFTs		Likely not clinically relevant
Antifungal	Micafungin/echinocandin [17]	CSA	Micafungin is a mild inhibitor of CYP3A4 in vitro; CSA is a CYP3A4 substrate	Concomitant use results in slightly increased CSA exposure	Titrate CSA; utilize whole blood CSA concentrations
Antifungal	Micafungin/echinocandin [36]	SIR	Unknown	SIR AUC is increased by 21 %; no effect on SIR C_{max}	Titrate SIR; utilize whole blood SIR concentrations
Antibacterial	Aminoglycosides [81]	CSA/TAC/SIR/EVR	Additive nephrotoxicity	Increases risk of kidney injury	Monitor CSA/TAC/SIR/EVR concentration and kidney function

(continued)

TABLE 4-3. (continued)

Anti-infective category	Anti-infective agent/class	Immunosuppressive agent or group of agents	Interaction	Clinical effect	Management
Antibacterial	Chloramphenicol [82–85]	CSA	Potential inhibition of CYP3A4 and 2C9 (rapid onset)	Increases CSA concentration by about 50%	Monitor CSA concentration and kidney function
Antibacterial	Quinolone antibiotics [37]: ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin	CSA	Inhibition of CYP3A4	Increases CSA concentration	Monitor CSA concentration
Antibacterial	Quinolone antibiotics [86]: ciprofloxacin ofloxacin levofloxacin moxifloxacin	TAC	Inhibition of CYP3A4	Increases TAC concentration	Likely not clinically relevant; monitor TAC concentration
			Additive QTc prolongation	Increases risk of torsade de pointes	Monitor electrocardiogram for QTc prolongation
Antibacterial	Quinolone antibiotics [20]: ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin	SIR	Inhibition of CYP3A4	Increases SIR concentration	Uncertain clinical significance; monitor SIR concentration
Antibacterial	Linezolid, tedizolid [87]	AZA/MMF	Additive bone marrow suppression	Increased risk of thrombocytopenia, leukopenia, and anemia	Monitor CBC and use limited course or select alternatives
Antibacterial	Macrolide antibiotics: clarithromycin [48–50], erythromycin [51–53], telithromycin, azithromycin	CSA/TAC/SIR/EVR	Inhibition of CYP3A4	Significant increase in CSA/TAC/SIR concentrations	Avoid concomitant use whenever possible; consider azithromycin [54] If coadministration is necessary, empirically reduce CSA/TAC/SIR/EVR doses, monitor CSA/TAC/SIR/EVR whole blood concentrations; titrate CSA/TAC/SIR/EVR dose
		TAC	Additive QTc prolongation	Increases risk of torsade de pointes	Monitor electrocardiogram for QTc prolongation
Antibacterial	Metronidazole [37, 88]	CSA/TAC	Inhibition of CYP3A4	Increases CSA/TAC concentration	Monitor CSA/TAC concentration
Antibacterial	Nafcillin [89]	CSA	Unknown mechanism	Increases CSA concentration	Monitor CSA concentration
Antibacterial	Rifampin [32]	MMF	Unknown	Major reduction in MPA $AUC_{0-12\ h}$	Consider MPA drug monitoring while on rifampin [90]
Antibacterial	Rifampin/rifabutin	MMF	Induction of the uridine diphosphate glucuronosyl transferase in the kidney, liver, and intestines		
Antibacterial	Rifampin [15, 20, 39, 40]	CSA/TAC/SIR/EVR	Induction of CYP3A4-mediated CSA/TAC/SIR/EVR metabolism	Decrease in plasma CSA/TAC/SIR/EVR concentrations	Titrate CSA/TAC/SIR/EVR dose; utilize CSA/TAC/SIR/EVR whole blood concentrations Consider rifabutin if appropriate [41]
Antihepaciviral	Protease inhibitors [61]: boceprevir, telaprevir	CSA/TAC/SIR/EVR	CYP3A4 inhibition	Significant increase in CSA/TAC/SIR/EVR concentrations	When initiating CSA/TAC/SIR/EVR, use low doses, and utilize whole blood concentrations to determine the dosing interval; may need to utilize liquid formulations to achieve small oral doses Titrate CSA/TAC/SIR/EVR dose and/or interval; utilize CSA/TAC/SIR/EVR whole blood concentration

Antihepaciviral	Protease inhibitor [91, 92]: simeprevir	CSA	Possible intestinal CYP3A4/P-gp inhibition by simeprevir Inhibition of CYP3A4 and P-gp by CSA	Increase in both simeprevir and CSA concentrations	Monitor CSA whole blood concentration Monitor for increased side effects of simeprevir or avoid combination
		TAC	Unknown	May decrease TAC concentrations	Minimal clinical significance Monitor TAC whole blood concentration
Antiviral	Acyclovir, ganciclovir [27, 34]	MMF	The antiviral and MPAG compete for renal tubular secretion; particularly in renal impairment	Risk for increased acyclovir, ganciclovir, and MPAG concentrations (evidence of increased antiviral levels)	Use combination with caution in renal insufficiency; monitor CBC
Antiviral	Foscarnet [93]	CSA/TAC/SIR/EVR	Additive nephrotoxicity	Increases risk of kidney injury	Monitor CSA/TAC/SIR/EVR concentration and kidney function
Antiretroviral	NNRTI: efavirenz, etravirine, nevirapine [15, 58, 94, 95]	CSA/TAC/SIR/EVR	Induction of CYP3A4-mediated CSA/TAC/SIR/EVR metabolism	Decrease in plasma CSA/TAC/SIR concentrations	Titrate CSA/TAC/SIR/EVR dose; utilize CSA/TAC/SIR/EVR whole blood concentrations
Antiretroviral	Nevirapine [30]	MMF	Competition for and/or altered enterohepatic recycling	Slight but significant reduction in nevirapine exposure; unknown effect on MPA	No recommendations have been made
Antiretroviral	Anti-HIV protease inhibitors [58]: amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir [59, 60], nelfinavir, ritonavir [59, 60], saquinavir	CSA/TAC/SIR/EVR	CYP3A4 inhibition	Significant increase in CSA/TAC/SIR/EVR concentrations	When initiating CSA/TAC/SIR/EVR, use low doses, and utilize whole blood concentrations to determine the dosing interval; may need to utilize liquid formulations to achieve small oral doses Titrate CSA/TAC/SIR/EVR dose and/or interval; utilize CSA/TAC/SIR/EVR whole blood concentration

Efavirenz: induction increases (more rapid CL) TAC and CSA and prednisolone.

Abbreviations: *CSA* cyclosporine (Neoral, Sandimmune), *TAC* tacrolimus (Prograf, Astagraf XL), *SIR* sirolimus (Rapamune), *EVR* everolimus (Zortress), *MMF* mycophenolate mofetil (CellCept), *AZA* azathioprine (Imuran), *HIV* human immunodeficiency virus, *HCV* hepatitis C virus.

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