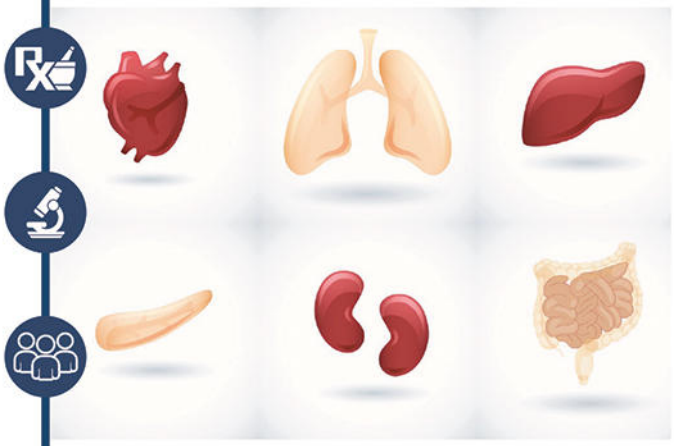
AMERICAN SOCIETY OF® TRANSPLANTATION

COMPREHENSIVE TRAINEE CURRICULUM



COMPREHENSIVE TRAINEE CURRICULUM

WATCH 52 ONLINE LESSONS INCLUDING:

- *Adult and Pediatric Liver*
- *Adult Cardiac and Pulmonary*
- *Abdominal Transplant Surgery*
- *Cardiothoracic Transplant Surgery*
- *Adult and Pediatric Kidney*
- *Transplant Pharmacy*

Solid organ transplantation is a multidisciplinary field, leading to a diverse community of professionals within the AST. As a result, it is often necessary for trainees to have extensive knowledge of all areas of transplantation—not just their specialty.

Check out this brand new resource, meant to supplement the training trainees and fellows receive at their university or hospital.

$50 members / $200 non-members

AMERICAN SOCIETY OF TRANSPLANTATION

Received: 30 January 2019 | Accepted: 12 February 2019

DOI: 10.1111/ctr.13510

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

WILEY Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

Interactions between anti-infective agents and immunosuppressants—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Tracy Sparkes[1] | **Tracy L. Lemonovich**[2] **on behalf of the AST Infectious Diseases Community of Practice**

[1]Department of Pharmacy, University of Maryland Medical Center, Baltimore, Maryland

[2]Division of Infectious Diseases and HIV Medicine, Department of Medicine, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, Ohio

Correspondence
Tracy Sparkes, Department of Pharmacy, University of Maryland Medical Center, Baltimore, MD.
Email: tsparkes@umm.edu

Funding information
American Society of Transplantation

Abstract

These updated guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation provide an update on potential drug-drug interactions between anti-infectives and immunosuppressants, which are most notable with calcineurin and mTOR inhibitors. Drug-drug interactions may occur through pharmacokinetic mechanisms leading to altered drug concentrations of either the anti-infective or immunosuppressive drug, or by pharmacodynamic interactions increasing or decreasing the efficacy or toxicity of the medications. Many of the significant pharmacokinetic interactions occur through inhibition or induction of the cytochrome 3A4 system by anti-infective agents leading to increased or decreased immunosuppressive agent levels, respectively. The membrane transporter P-glycoprotein is also often involved in drug interactions. Since the last iteration of these guidelines, multiple new hepatitis C virus direct-acting antivirals have become available for use in SOT recipients. Of these agents, some are substrates of cytochrome and drug transporter systems, while others inhibit these systems and may affect immunosuppressive agents. Due to the high risk for drug-drug interactions in the solid organ transplant population, practitioners must be aware of potential interactions and be vigilant in monitoring and adjusting drug dosing when appropriate.

KEYWORDS
antifungals, antimicrobials, antiviral, drug interactions, immunosuppressants, organ transplant

1 | INTRODUCTION

Solid organ transplant recipients may be affected by infectious complications at any point during their post-transplant course. In addition to efficacy considerations, the optimal treatment must also be guided by knowledge of the effects of the anti-infective agent on the pharmacokinetics and/or pharmacodynamics of the immunosuppressants that the patient is receiving. Drug-drug interactions between immunosuppressants and anti-infective agents can be divided into two categories: pharmacokinetic and pharmacodynamic interactions. Pharmacokinetic drug-drug interactions may lead to altered drug concentrations of immunosuppressants, anti-infective agents, and/or their metabolites through interactions in stages of absorption, distribution, metabolism, or elimination. Pharmacodynamic interactions may occur due to drugs increasing or decreasing the efficacy or toxicity of each other and may lead to either detrimental or beneficial drug interactions.

Some of the most frequently used immunosuppressive agents in organ transplantation are metabolized via the cytochrome (CYP) 3A4 system. Immunosuppressive drug interactions can be caused by

TABLE 1 Anti-infective and immunosuppressant drug interactions

Antimicrobial	Immunosuppressant	Severity of Interaction[a]	Interaction	Mechanism of interaction	Suggested actions	GRADE[b]
Antibacterials						
Macrolides						
Erythromycin	CSA, TAC, **SRL**, EVR	+++	↑ Imm levels	CYP3A4 inhibition	Avoid/↓ Imm up to 1/2	Strong, Moderate
	Methylprednisolone	++		CYP3A4 inhibition	Utilize prednisone or azithromycin for prolonged courses	Strong, Low
Clarithromycin	CSA, TAC, **SRL**, **EVR**	+++		CYP3A4 inhibition	Avoid/↓ Imm by 1/2	Strong, Moderate
	Methylprednisolone	++		CYP3A4 inhibition	Utilize prednisone or azithromycin for prolonged courses	Strong, Low
Azithromycin	CSA, TAC, SRL, EVR	±		CYP3A4 inhibition	No adjustment	Strong, Moderate
Rifamycins						
Rifampin	CSA, TAC, **SRL**, EVR	+++	↓ Imm levels	CYP3A4 induction	Avoid/↑ Imm 2-fold and monitor	Strong, Moderate
	MMF, MPA	+		Induction of UGT and organic anion transporters	Utilize alternate rifamycin if possible	Strong, Moderate
	Prednisone	++		CYP3A4 induction	Monitor steroid efficacy, consider dose increase	Strong, Low
Rifabutin	CSA TAC, **SRL**, **EVR**	++		CYP3A4 induction	Monitor Imm levels	Strong, Moderate
Rifapentine	CSA, TAC, SRL, EVR, Prednisone	++		CYP3A4 induction	Monitor Imm levels	Weak, Very Low
Aminoglycosides						
Gentamicin	CSA, TAC	+++	Enhanced nephrotoxicity	Pharmacodynamic	Avoid/Monitor renal function	Strong, Low
Tobramycin						
Amikacin						
Streptomycin						
Fluoroquinolones						
Ciprofloxacin, Ofloxacin, Levofloxacin, Moxifloxacin	CSA, TAC	++	QTc Prolongation	Pharmacodynamic	Monitor QTc and Electrolytes	Strong, Very Low
	Prednisone, Methylprednisolone	++	Tendonitis, Tendon Rupture	Pharmacodynamic	Monitor	Strong, Moderate
Ciprofloxacin	MMF, MPA	±	May ↓ Imm levels	Impaired conversion to MPA	Monitor	Weak, Very Low
Other antibacterials						
Nafcillin	CSA, TAC, SRL, EVR	+	↓ Imm levels	CYP3A4 induction	Monitor Imm levels	Strong, Low
Quinupristin/Dalfopristin	CSA, Expected for TAC, SRL, EVR	+++	↑ CSA	CYP3A4 inhibition	Monitor Imm levels	Strong, Low

(Continues)

TABLE 1 (Continued)

Antimicrobial	Immunosuppressant	Severity of Interaction[a]	Interaction	Mechanism of interaction	Suggested actions	GRADE[b]
Chloramphenicol	CSA, TAC, Expected for SRL, EVR	++	↑ Imm Levels	Suspected CYP3A4 inhibition	↓ CSA or TAC by 25%	Strong, Low
Tigecycline	CSA	±	↑ Tigecycline	P-gp substrate	Monitor Imm levels	Weak, Very Low
Metronidazole	CSA, TAC, SRL, EVR	±	May ↑ Imm Levels	Mild CYP3A4 inhibition	No adjustment	Weak, Very Low
	MMF, MPA	+	May ↓ Imm levels	Interference with enterohepatic recirculation	Monitor	Weak, Low
Clindamycin	CSA, TAC, SRL, EVR	±	May ↓ Imm levels	Suspected CYP3A4 induction	No adjustment/consider monitor levels	Weak, Very Low
Linezolid	MMF, MPA, AZA, SRL, EVR	++	Myelosuppression	Pharmacodynamic	Monitor WBC and platelets	Strong, Very Low
Sulfamethoxazole-trimethoprim and other sulfonamides	MMF, MPA, AZA, SRL, EVR	++	Myelosuppression	Pharmacodynamic	Monitor WBC, hematocrit, platelets	Strong, Very Low
	CSA, TAC	++	Nephrotoxicity	Pharmacodynamic	Monitor renal function	Strong, Low
Antimalarials						
Artemether/Lumefantrine	CSA, TAC, SRL, EVR	+	↓ Imm levels	CYP3A4 induction (Artemether component)	Monitor Imm levels	Weak, Very Low
Antifungals						
Azole antifungals						
Ketoconazole	CSA, TAC, **SRL, EVR**	+++	↑ Imm levels	CYP3A4 inhibition	Avoid/↓ Imm by 1/2	Strong, Moderate
	Methylprednisolone	++	↑ Imm levels	CYP3A4 inhibition	↓ Imm by 1/2	Strong, Moderate
Voriconazole	CSA, TAC, **SRL, EVR**	+++		CYP3A4 inhibition	↓ CSA by 1/2, ↓ Tac by 2/3	Strong, Moderate
	Methylprednisolone	+		CYP3A4 inhibition	Monitor	Weak, Very Low
Itraconazole	CSA, TAC, SRL, EVR	+++		CYP3A4 inhibition	↓ Imm by 1/2, Monitor Imm Levels	Strong, Moderate
	Methylprednisolone	++		CYP3A4 inhibition	↓ Imm by 1/2	Strong, Moderate
Posaconazole	CSA, TAC, **SRL**, EVR	+++		CYP3A4 inhibition	↓ CSA by 1/4, ↓ Tac by 2/3	Strong, Moderate
	Methylprednisolone	+		CYP3A4 inhibition	Monitor	Weak, Very Low
Isavuconazole	CSA, TAC, SRL, EVR,	++		CYP3A4 inhibition	Monitor Imm levels	Strong, Moderate
	MMF, MPA	±		UGT inhibition	Monitor for MMF, MPA ADE's	Weak, Low
Fluconazole	CSA, TAC, SRL,EVR	++		CYP3A4 inhibition	Dose dependent	Strong, Moderate
Clotrimazole	CSA, TAC, SRL, EVR	++		CYP3A4 inhibition	Monitor Imm Levels	Strong, Moderate
Echinocandins						
Caspofungin	CSA	++	↑ Caspofungin levels	Unknown	Monitor AST/ALT	Weak, Very Low
	TAC, No data on SRL, EVR	±	May ↓ TAC levels	Unknown	No Adjustment	Weak, Very Low

(Continues)

TABLE 1 (Continued)

Antimicrobial	Immunosuppressant	Severity of Interaction[a]	Interaction	Mechanism of interaction	Suggested actions	GRADE[b]
Micafungin	CSA	++	↓ CSA levels	Unknown	Monitor Imm levels	Weak, Low
	SRL	+	↑ SRL levels	Mild CYP3A4 inhibition	Monitor Imm levels	Weak, Low
Anidulafungin	CSA	+	↑ Anidulafungin levels	Unknown	None	Strong, Low
Polyenes						
Amphotericin B	CSA, TAC	++	Nephrotoxicity	Pharmacodynamic	Monitor renal function, Utilize lipid-based products if appropriate	Strong, Low
Other antifungals						
Flucytosine	MMF, MPA, AZA, SRL, EVR	++	Myelosuppression	Pharmacodynamic	Monitor WBC, hematocrit, platelets	Strong, Very Low
Antiviral agents						
Antivirals (non-HIV and non-HCV)						
Acyclovir	MMF, MPA	±	↑ Acyclovir in presence of renal impairment	Competition for renal tubular secretion	None	Strong, Low
Intravenous acyclovir	CSA, TAC	+++	Nephrotoxicity	Pharmacodynamic	Monitor renal function	Strong, Very Low
Ganciclovir, Valganciclovir	MMF, MPA, AZA, SRL, EVR	++	Myelosuppression	Pharmacodynamic	Monitor WBC	Strong, Low
Ribavirin	**AZA**	+++	Accumulation of 6-methylthioinosine and myelotoxicity	IMPDH inhibition by Ribavirin	Avoid	Strong, Low
Foscarnet	CSA, TAC	+++	Nephrotoxicity ↓Ca ↓Mg	Pharmacodynamic	Avoid/Monitor renal function, Ca, Mg	Strong, Low
Cidofovir	CSA, TAC	+++	Nephrotoxicity	Pharmacodynamic	Avoid/Monitor renal function	Strong, Very Low
Leflunomide	MMF, MPA, AZA	+++	Myelosuppression	Pharmacodynamic	Avoid/Monitor WBC, hematocrit and platelets	Strong, Very Low
Letermovir	CSA	+++	↑ CSA, ↑ Letermovir	CYP3A4 inhibition by Letermovir Inhibition of liver transporters, including ATP-binding cassette transporters and solute transporters by CSA	Decrease Letermovir to 240mg once daily in combination with CSA, Monitor Imm levels	Strong, Low
	TAC	+++	↑ TAC	CYP3A4 inhibition by Letermovir	Monitor Imm levels	Strong, Low
	SRL, EVR Expected	+++	↑ SRL	CYP3A4 inhibition by Letermovir	Monitor Imm levels	Strong, Low

(Continues)

TABLE 1 (Continued)

Antimicrobial	Immunosuppressant	Severity of Interaction[a]	Interaction	Mechanism of interaction	Suggested actions	GRADE[b]
Antiretroviral agents						
Protease inhibitors						
Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinavir/ritonavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir/ritonavir	CSA, TAC, SRL, **EVR**	+++	↑ Imm levels	CYP3A4 inhibition	Avoid if possible CSA 25-50 mg daily TAC 1 mg once or twice a week SRL 1 mg once or twice a week Monitor Imm levels	Strong, Moderate
	Prednisone	++		CYP3A4 inhibition	Monitor for symptoms of Cushing's syndrome	Strong, Low
Cytochrome P450 inhibitor						
Cobicistat	CSA, TAC, SRL, EVR	+++	↑ Imm levels	CYP3A4 inhibition	Avoid if possible TAC 0.5-1.5 mg once or twice a week Monitor Imm Levels	Strong, Low
Non-nucleoside reverse transcriptase inhibitors						
Efavirenz	CSA, TAC, SRL, EVR	++	↓ Imm levels	CYP3A4 induction	Monitor Imm Levels	Strong, Moderate
Nevirapine, Etravirine	CSA, TAC, SRL, EVR	±	May ↓ Imm levels	CYP3A4 Induction	Monitor Imm Levels	Strong, Low
Delavirdine	CSA, TAC, SRL,EVR	++	↑ Imm levels	Mild CYP3A4 Inhibition	Monitor Imm Levels	Strong, Very Low
Nucleoside reverse transcriptase inhibitors						
Tenofovir disoproxil fumarate	CSA, TAC	++	Nephrotoxicity	Pharmacodynamic	Monitor, consider tenofovir alafenamide	Weak, Very Low
Stavudine, Zidovudine	MMF/MPA	±	In vitro antagonism	Unknown	None	Weak, Very Low
Hepatitis C virus direct acting antivirals[c]						
Paritaprevir/ritonavir/ombitasvir + dasabuvir (PrOD)	CSA	+++	5.8-fold ↑ in CSA AUC	CYP3A4 inhibition	Use 1/5 CSA, monitor CSA levels	Strong, Low
	TAC	+++	57-fold ↑ in TAC AUC	CYP3A4 inhibition	Avoid	Strong, Low
	SRL	+++	38-fold ↑ in SRL AUC	CYP3A4 inhibition	Avoid	Strong, Low
	EVR	+++	27-fold ↑ in EVR AUC	CYP3A4 inhibition	Avoid	Strong, Low
Elbasvir/grazoprevir (EBR/GZR)	**CSA**	+++	15-fold ↑ in GZR AUC and 2-fold ↑ in EBR AUC	OATP1B inhibition	Avoid	Strong, Low
	TAC	++	43% ↑ in TAC AUC	Weak CYP3A4 inhibition by Grazoprevir	Monitor TAC levels	Strong, Low
	SRL, EVR	+	↑ Imm (not studied)	Weak CYP3A4 inhibition by Grazoprevir	Monitor Imm levels	Weak, Very Low

(Continues)

TABLE 1 (Continued)

Antimicrobial	Immunosuppressant	Severity of Interaction[a]	Interaction	Mechanism of interaction	Suggested actions	GRADE[b]
Sofosbuvir/velpatasvir (SOF/VEL)	CSA, TAC, SRL, EVR	+	↑ Imm	Weak P-gp Inhibition by velpatasvir	Monitor Imm levels	Weak, Low
Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX)	**CSA**	+++	9.4-fold ↑ in VOX AUC	OATP Inhibition	Avoid, VOX and CSA combination not recommended	Strong, Low
	TAC, SRL, EVR	+	↑ Imm	Weak P-gp inhibition by velpatasvir	Monitor Imm levels	Weak, Very Low
Glecaprevir/pibrentasvir (GLE/PIB)	CSA	+++	5-fold ↑ in GLE AUC with higher doses (400 mg) of CSA 5-fold ↑ in PIB AUC with higher doses of CSA	Inhibition of OATP1B	Not recommended in patients requiring stable CSA doses > 100 mg/day	Strong, Low
	TAC	+	1.45-fold ↑ in TAC AUC	Inhibition of P-gp and CYP3A4	Monitor Imm levels	Strong, Low
	SRL, EVR	+	↑ Imm (not studied)	Inhibition of P-gp and CYP3A4	Monitor Imm levels	Weak, Very Low
Simeprevir (SMP)	**CSA**	+++	5.8-fold ↑ in Simeprevir with CSA	Inhibition of OATP1B1, P-gp, and CYP3A	Avoid, Simeprevir and CSA combination not recommended	Strong, Moderate
	TAC	+	1.85-fold ↑ in Simeprevir exposure, ↓ TAC	Inhibition of OATP1B1	Monitor TAC levels	Strong, Moderate
	SRL, EVR	+	Potential ↑ or ↓ in Imm levels	CYP3A4 and P-gp inhibition	Monitor Imm levels	Strong, Low

AZA, Azathioprine; CSA, cyclosporine; EVR, everolimus; Imm, immunosuppressant; IMPDH, inosine monophosphate dehydrogenase; MMF, mycophenolate mofetil; MPA, mycophenolic acid; OATP, organic anion-transporting polypeptide; SRL, sirolimus; TAC, tacrolimus

Data on EVR not always present, but is included in the table on the basis of a similar route of metabolism to other immunosuppressants involved in drug-drug interactions.

Drugs in bold are contraindicated

[a]Severity of Interaction. +++, severe interaction, use alternative drug if possible, otherwise monitor levels of immunosuppressant or for potential toxicity and modify dose accordingly; ++, moderate interaction, requires monitoring levels or potential toxicity, and may require modification of immunosuppressant dosing; +, minor interaction or does not have major toxicity; ±, in vitro data and/or case reports have reported an interaction, but changes in immunosuppressive levels have not been consistently seen in clinical practice

[b]GRADE: Strength of Recommendation (Strong, Weak) and Quality of the Evidence (High, Moderate, Low, Very Low)

[c]Table partially modified from: AASLD-IDSA. Patients Who Develop Recurrent HCV Infection Post Liver Transplantation. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. [Accessed July 8 2018].

an anti-infective agent directly inhibiting CYP3A4 or via drug competition for CYP3A4 substrate sites. Both of these mechanisms may result in increased immunosuppressive concentrations. In contrast, CYP3A4 induction via increased synthesis or decreased breakdown of CYP isoenzymes may result in decreased immunosuppressive concentrations.[1] The membrane transporter P-glycoprotein (P-gp) is also involved in drug interactions between immunosuppressants and anti-infective agents.[2] Drugs that inhibit or induce P-gp activity can ultimately result in increased or decreased bioavailability in the intestine. Moreover, due to genetic polymorphisms, patients may express variation in CYP3A4 and CYP3A5 enzymes and P-gp which can also influence drug levels. The timing of the drug interaction will depend on the mechanism of the interaction. For example, CYP inhibition occurs quickly, whereas CYP induction can take up to 14 days to manifest, as this requires the upregulation of CYP enzymes.[3] Therefore, knowledge of the mechanism of the interaction, in addition to individual pharmacokinetic properties of the drug, such as elimination half-life, is necessary to best predict the timing that the effect is expected. Monitoring and subsequent dose adjustments should account for these factors in order to maintain safe and effective therapy for organ transplant recipients.[1,2,4]

Pharmacodynamic drug interactions can be caused by additive, synergistic, or antagonistic effects.[5] Pharmacodynamic interactions within transplantation are varied and may include myelosuppression, gastrointestinal intolerance, electrolyte abnormalities, and nephrotoxicity. Similar to pharmacokinetic interactions, monitoring is a crucial component of maintaining safe therapy.

The following Table 1 provides summary information on interactions between anti-infectives and immunosuppressants, an indication of their severity, the mechanism of the interaction, suggested actions by the clinician, and the grade of evidence supporting these effects. For completeness, we have also included anti-infective agents in the table that may not always result in significant interactions in clinical practice but have either in vitro data demonstrating an interaction with immunosuppressants or case reports demonstrating evidence of an interaction. The following discussion describes these interactions in more detail, focusing on the most severe, with suggested approaches for management.

2 | INTERACTIONS THAT SIGNIFICANTLY RAISE CALCINEURIN INHIBITOR AND MTOR INHIBITOR PLASMA LEVELS

2.1 | Macrolide antibiotics

Macrolide antibiotics, with the exception of azithromycin, are moderate to strong inhibitors of CYP3A4 and thus decrease the metabolism of calcineurin inhibitors (CNI): cyclosporine (CSA) and tacrolimus (TAC), and mammalian target of rapamycin (mTOR) inhibitors: sirolimus (SRL) and everolimus (EVR).[6] Concomitant use of erythromycin or clarithromycin with CNI or mTOR inhibitors results in significant (3-10 fold) increases in immunosuppressant concentration or area under the curve (AUC). The availability of azithromycin, which has fewer gastrointestinal side effects, has resulted in diminished use of erythromycin and clarithromycin, thereby reducing the chance of inadvertent coadministration. However, erythromycin is sometimes utilized in patients with impaired gastric emptying or ileus. The coadministration of erythromycin with CNI, and especially mTOR inhibitors, should be avoided in this situation when feasible; however, if the combination is used, we recommend up to a 50% reduction of CNI or mTOR inhibitor upon initiation, since the effect is rapid. Daily drug level monitoring with CNI and EVR and every third day level monitoring with SRL is recommended. Similar considerations apply to clarithromycin. However, this agent should be avoided whenever possible due to the interactions previously noted, with several recent case reports in the literature related to CNI and mTOR toxicity associated with clarithromycin use.[7-9] The majority of in vitro and in vivo data indicate there is no pharmacokinetic interaction between azithromycin and CNI or mTOR inhibitors. While two case reports describe elevation of CSA concentrations with several days of concomitant administration of azithromycin, an additional study reports no clinically relevant increase.[10-12] Elevation of TAC levels has also been reported with coadministered azithromycin, but is limited to one case report.[13] Therefore, monitoring drug levels may be appropriate. Fidaxomicin, a macrolide antibiotic indicated for *Clostridium difficile*-associated diarrhea, undergoes minimal systemic absorption and is metabolized independently of CYP enzymes. Although fidaxomicin is a substrate of P-gp, use with CSA did not result in increases in exposure that were significant enough to warrant fidaxomicin dosage adjustment per product labeling.[14]

2.2 | Antifungal agents

All of the azole antifungals are CYP3A4 inhibitors and result in decreased metabolism of both CNI and mTOR inhibitors.[15] This ultimately leads to increases in concentration and AUC, although the potency of the interaction is different for each agent. Ketoconazole, itraconazole, posaconazole, and voriconazole have been shown to be more potent inhibitors of CYP3A than are isavuconazole, fluconazole, or clotrimazole.[16,17] Additionally, some of the azoles are also P-gp inhibitors, although to varying degrees, which further contributes to interactions.[15,18]

Ketoconazole has been shown to be the most potent CYP3A4 inhibitor among the azoles, resulting in AUC increases in TAC, CSA, SRL, and EVR up to 15-fold.[19] Dose reductions by at least half of the current dosing are recommended, in addition to close monitoring. In some circumstances, this interaction with CNI and mTOR inhibitors has been used advantageously in an effort to decrease immunosuppressive dose requirements and medication cost to transplant recipients.[20-23] If undertaken, this drug combination must be carefully monitored as inadvertent discontinuation of ketoconazole by the patient or an outside healthcare provider will dramatically decrease immunosuppressive levels, potentially increasing the risk for rejection. Although less potent of an interaction, itraconazole dose reductions are also recommended when used with CNI.[24-27] Although itraconazole is not recommended with SRL or EVR per product labeling,

use has been documented, and dose reductions and monitoring are warranted.[28-31]

The interaction of fluconazole with CNI and mTOR inhibitors is both dose- and drug-dependent.[32] At modest doses (100-200 mg/d), fluconazole effects on CSA are minor, while moderate increases are seen with TAC and mTOR inhibitors. At higher doses of fluconazole required for systemic fungal infections, more significant dose reductions of immunosuppressants may be required.

Voriconazole prescribing information recommends empiric dose reduction of TAC by two-thirds and CSA by 50% of the original maintenance dose when voriconazole is initiated.[18,33,34] The combination of voriconazole and SRL is contraindicated as SRL levels may rapidly rise 10-fold.[18] However, a small case series reported that voriconazole and SRL could potentially be used together if low doses of SRL are used (0.5-1.0 mg/d).[35] Similarly, EVR prescribing information recommends that it not be administered with voriconazole, but case reports have detailed their concurrent use with EVR dose reduction.[19,36,37] Posaconazole prescribing information recommends empiric dose reduction of TAC by two-thirds and to decrease CSA dose by one-fourth of the original maintenance dose when posaconazole is initiated.[38,39] The combination of posaconazole and SRL is contraindicated per labeling due to a 9-fold increase in SRL; however, it has been used in clinical practice with dose reduction and careful monitoring.[38,40] No information is available on the use of EVR and posaconazole in the prescribing information of either agent, but one case report in a renal transplant recipient found a 3.8-fold increase in EVR levels with posaconazole.[19,36,38] Additionally, it should be noted that posaconazole oral suspension and the newer delayed-release tablets are not interchangeable. While posaconazole product information does not differentiate CNI or mTOR interactions between the formulations, one study notes a significant increase in the TAC concentration/dose ratio when posaconazole delayed released tablets were utilized in lung transplant recipients.[41] Close drug monitoring is recommended upon initiation, during, and after discontinuation of voriconazole or posaconazole. We suggest monitoring approximately 1 week after discontinuation, with continued monitoring at least weekly until immunosuppression has stabilized.[42]

Isavuconazole prescribing information recommends use with caution in combination with TAC, CSA, and SRL due to the expected increase in CNI and mTOR exposure. Although TAC exposure was increased 2.25-fold in one study, a retrospective study reported a more modest change with a TAC dose decrease requirement of 1.3-fold.[43,44] Product labeling for isavuconazole does not make a TAC dose adjustment recommendation, and published reports range from a suggested empiric reduction of 50% to no reduction with close therapeutic drug monitoring.[44,45] Exposure to CSA and SRL was also increased by 29% and 84%, and this effect is expected for EVR, although not described. Additionally, when used with a mycophenolate product, mycophenolate exposure may be increased through inhibition of uridine diphosphate-glucuronosyltransferases (UGT). Therefore, monitoring for gastrointestinal and hematologic toxicity is warranted.[43]

Oral clotrimazole troches used for oral mucocutaneous candidiasis prophylaxis or treatment have also been shown to increase TAC and SRL blood levels, doubling levels in some studies.[46-51] The mechanism of this interaction is also thought to be CYP3A4-mediated. While this interaction has not been clearly documented for CSA or EVR, it is expected, and CNI and mTOR inhibitor levels should be monitored during initiation or discontinuation of clotrimazole.

Azole antifungals are also capable of affecting certain corticosteroids utilized in transplantation, primarily methylprednisolone. The majority of the evidence for this interaction is derived from use with ketoconazole and itraconazole, in which an increased methylprednisolone AUC of 135% with ketoconazole and a 2.6-fold increase in AUC with itraconazole was observed, in addition to decreases in cortisol.[52,53] Due to these effects, a 50% reduction in methylprednisolone dose is recommended when used together as long-term therapy.[54] While not described in the literature, similar effects with voriconazole and posaconazole may be expected; therefore, consideration for methylprednisolone dose reduction and monitoring is warranted if coadministered for extended periods of time. Conversely, prednisone and prednisolone have been shown to not be significantly affected by ketoconazole, itraconazole, or isavuconazole.[43,55-59] No data are available for voriconazole or posaconazole; however, no interaction would be expected.

Of note, the echinocandin antifungal agents, caspofungin, micafungin, and anidulafungin, provide an intravenous alternative when clinically appropriate. As none are significantly metabolized by CYP3A4, clinically significant drug interactions are not anticipated.

2.3 | Antiretroviral therapy

Patients infected with human immunodeficiency virus-1 (HIV-1) are increasingly undergoing organ transplantation.[60,61] Interactions between antiretroviral therapy and immunosuppressants can lead to profound increases in CNI and mTOR levels, most notably when ritonavir or cobicistat is used.[62,63] Both agents are used as pharmacologic boosters and are inhibitors of CYP3A4 as well as P-gp. Ritonavir coadministration with tacrolimus has been shown to necessitate tacrolimus dose reductions of up to 120-fold.[64] Cobicistat product labeling acknowledges the interaction with CNI and mTOR inhibitors and recommends therapeutic drug monitoring of the immunosuppressant agent.[65] However, two case reports detailing tacrolimus use with cobicistat noted significant elevations in tacrolimus levels with resultant acute kidney injury, with a tacrolimus dose reduction of approximately 98% required in one patient.[66,67] Avoidance of ritonavir and cobicistat-based antiretroviral regimens is recommended, especially as a recent study associated PI-based regimens with an increased risk of graft loss and death.[68] Additionally, integrase inhibitor-based regimens offer an opportunity for post-transplant regimens with no expected drug-drug interactions.[69-71] Immunosuppression and antiretroviral therapy drug interactions are

summarized in the table; however, the reader is also referred to the *Solid Organ Transplant in the HIV-Infected Patient* chapter within these guidelines for further detail.

2.4 | Antiviral agents

Letermovir is an antiviral with a novel mechanism of action as an inhibitor of the cytomegalovirus (CMV) terminase complex and is indicated for the prophylaxis of CMV infection in allogeneic hematopoietic stem cell transplant recipients.[72] Studies are currently ongoing for use in solid organ transplant (SOT) recipients. It is a substrate of CYP3A4; CSA, TAC, SRL, and letermovir levels are increased by concomitant use. Letermovir product information recommends decreasing letermovir dosing to 240 mg once daily when given with CSA. CSA, TAC, and SRL levels should be monitored during and after discontinuation of letermovir.[73] No data on EVR have been reported, but the potential to increase EVR levels seems likely and drug monitoring is recommended. There are no significant pharmacokinetic drug-drug interactions with valganciclovir or acyclovir.

2.5 | Hepatitis C virus (HCV) direct acting antivirals (DAA)

The newer direct acting antivirals (DAAs) are important for treatment of hepatitis C infection after liver and other solid organ transplantation and require consideration of potentially significant drug interactions. Multiple new DAAs and combinations have become available since the last iteration of these guidelines. Most drug interactions are with the CNI and mTOR inhibitors due to many DAAs being substrates of CYP3A4 and other cytochromes, but these interactions may be difficult to predict.[74,75] The combination may cause elevated DAA and/or CNI and mTOR inhibitor levels and therefore require close monitoring of immunosuppressant levels. CSA appears to have more interactions than TAC, and several DAA fixed combinations such as elbasvir/grazoprevir, sofosbuvir/velpatasvir/voxilaprevir, and simeprevir are not recommended to be given concomitantly with CSA.[74,76,77] Sofosbuvir and ledipasvir appear to have few clinically significant interactions in studies of SOT recipients but may require adjustment in immunosuppressant dosing, and monitoring of levels should be considered.[74,78,79] A detailed summary of interactions and suggested actions is included in the table, and the reader is also referred to the guideline chapter *Viral Hepatitis* for additional information.

3 | INTERACTIONS THAT SIGNIFICANTLY DECREASE CALCINEURIN INHIBITOR AND MTOR INHIBITOR PLASMA LEVELS

3.1 | Rifamycins

All of the rifamycins are strong inducers of CYP3A4. For rifampin and rifabutin, clinical data confirm the dramatic increases in clearance and resultant decreases in plasma levels of CNI and mTOR inhibitors.[80-86] This effect has been reported to remain even in the presence of multiple CYP3A4 inhibiting medications.[87] No clinical data in transplant recipients are available for rifapentine, but a similar effect is likely. This combination should be avoided if at all possible because of the difficulty of maintaining therapeutic levels of CNI and mTOR inhibitors. In those situations where a rifamycin derivative must be used, as in patients with active tuberculosis, increased doses of CNI or mTOR inhibitors should be initiated with the onset of combined therapy. We recommend a 2-fold dose increase upon the initiation of therapy, with rapid subsequent increases (up to 10-fold reported) and frequent drug level monitoring until stable dosing is achieved. Similar vigilance is required when rifamycin therapy is discontinued. Limited clinical experience in transplant recipients suggests that rifabutin is a less potent CYP3A4 inducer than rifampin and may be the preferred rifamycin in this patient population due to less drug-drug interactions.[82,88,89]

A much less dramatic effect on MMF pharmacokinetics has been reported with rifampin.[90] Although the decrease in MPA exposure appears to be moderate compared with those for CNI, the manufacturer's prescribing information recommends avoiding this combination when possible.[91] Steroid exposure can be significantly affected by coadministration with rifampin; therefore, monitoring for signs of steroid failure and a prednisone/prednisolone dose increase of up to 2-fold may be warranted.[92] Ethambutol and isoniazid, which are often used in combination with these agents, do not appear to interact with immunosuppressive agents.

3.2 | Antiretroviral therapy

In contrast to protease inhibitors, efavirenz, a non-nucleoside reverse transcriptase inhibitor, induces the metabolism of CSA, TAC, SRL, and EVR, often necessitating IS dose increases. Product labeling suggests close monitoring of IS levels for at least 2 weeks until stable concentrations are reached when starting or stopping treatment with efavirenz.[93] One pharmacokinetic study found CSA doses to be approximately 2 times higher when used with efavirenz; however, there are more limited data available for TAC and SRL.[62,94] A case report noted an EVR dose approximately 3 times higher than a typical dosing regimen when used with an efavirenz-containing regimen; however, no pharmacokinetic analysis was completed.[95]

3.3 | Costimulatory blockade

Belatacept, a selective T-cell costimulation blocker, is an intravenous maintenance immunosuppressive agent that was introduced in 2011. In healthy volunteers, it was not shown to alter the pharmacokinetics of drugs that are substrates of multiple CYP enzymes, including CYP3A4.[96] Therefore, interactions with immunosuppressive agents are not expected. However, in the setting of infection, when it is often appropriate to reduce immunosuppression, it should be noted that belatacept is a less titratable agent than other immunosuppressants.

4 | PHARMACODYNAMIC INTERACTIONS

The most concerning pharmacodynamic interaction among immunosuppressants and anti-infective agents is additive nephrotoxicity, which can be seen when CNI are used in conjunction with certain anti-infectives. This can be observed with the concomitant administration of CNI with aminoglycosides, amphotericin (including lipid formulations), cidofovir, foscarnet, intravenous acyclovir, and higher doses of sulfamethoxazole-trimethoprim.[97-99] Alternative therapies without nephrotoxicity should be utilized whenever possible. When nephrotoxic therapies are deemed essential to treatment, CNI should be minimized whenever possible. Renal function must be carefully monitored, and changes in renal function may necessitate decreasing or discontinuing anti-infective therapies. When TAC is utilized with certain anti-infectives, especially macrolide antibiotics, fluoroquinolones, and azole antifungals, there may be an increased risk of QTc prolongation. Monitoring of QTc and electrolytes is warranted if patients are receiving multiple agents known to prolong QTc.

Among antiproliferative immunosuppressants, the most prominent pharmacodynamic interaction with anti-infectives is additive myelosuppression. Administration of MMF, MPA, or azathioprine with leflunomide for BK virus nephropathy may result in additive myelosuppression. Therefore, we recommend to discontinue the antiproliferative agents upon initiation of leflunomide if possible. Additionally, antiviral agents such as ganciclovir and valganciclovir and antibacterials such as linezolid and sulfonamides may also result in myelosuppression when combined with these agents.[100] Careful monitoring of white blood cells, platelets, and hematocrit is necessary, with consideration of dose adjustments of immunosuppressive agents as applicable. Gastrointestinal intolerance is expected to be a common pharmacodynamic interaction when antimicrobials are used in conjunction with various immunosuppressive agents, especially MMF and MPA, although this interaction has not been well quantified in the literature.

Aside from high dose methylprednisolone, pharmacokinetic drug interactions with anti-infectives have not been identified for agents commonly utilized for induction immunosuppression or for agents used to treat rejection. However, pharmacodynamic interactions such as myelosuppression may be prominent among patients receiving lymphocyte-depleting induction therapy, such as rabbit anti-thymocyte globulin or alemtuzumab, and those receiving therapies for desensitization or rejection treatment.[101,102] Rituximab, bortezomib, carfilzomib, and eculizumab have all been reported to have potential to cause myelosuppression. Given their prolonged duration of effect, monitoring for myelosuppression is recommended, especially when antimicrobial agents are utilized with or subsequent to these therapies. Additionally, some of these agents have potential to decrease vaccine efficacy, and the reader is referred to the chapter entitled *Vaccination in Solid Organ Transplant* for additional information.

Pharmacodynamic interactions may also work in synergy. For example, the mTOR inhibitors may decrease the incidence and severity of cytomegalovirus post-transplant and MMF has been reported to potentially be associated with a decreased incidence of *Pneumocystis jiroveci* pneumonia.[103-105] Among HIV-infected transplant recipients, abacavir and mycophenolate may act synergistically to suppress replication of HIV.[106]

5 | CONCLUSION

In summary, solid organ transplant recipients are at high risk for drug-drug interactions, particularly between anti-infectives and immunosuppressants. Transplant practitioners must be vigilant in monitoring for potential interactions and making dose adjustments when appropriate, particularly upon initiation or discontinuation of therapy.

ACKNOWLEDGEMENTS

This manuscript was modified from the Guideline included in the 3rd Edition of the AST Infectious Diseases Guidelines written by Jennifer Trofe-Clark and Tracy L. Lemonovich published in the American Journal of Transplantation 2013;13 (Suppl 4): S318-326, and endorsed by the American Society of Transplantation

CONFLICT OF INTEREST

Tracy Sparkes has nothing to disclose. Tracy Lemonovich has served on a Medical Affairs Advisory Board for Allergan. The authors have not accepted funding or support for preparation of this manuscript.

ORCID

Tracy Sparkes https://orcid.org/0000-0001-8305-7296

REFERENCES

1. Glotzbecker B, Duncan C, Alyea E 3rd, Campbell B, Soiffer R. Important drug interactions in hematopoietic stem cell transplantation: what every physician should know. *Biol Blood Marrow Transplant*. 2012;18:989-1006.
2. Srinivas TR, Meier-Kriesche HU, Kaplan B. Pharmacokinetic principles of immunosuppressive drugs. *Am J Transplant*. 2005;5:207-217.
3. Lin JH, Lu A. Inhibition and induction of cytochrome P450 and the clinical applications. *Clin Pharmacokinet*. 1998;35:361-390.
4. Christians U, Jacobsen W, Benet LZ, Lampen A. Mechanisms of clinically relevant drug interactions associated with tacrolimus. *Clin Pharmacokinet*. 2002;41:813-851.
5. Roberts AG, Gibbs ME. Mechanisms and the clinical relevance of complex drug-drug interactions. *Clin Pharmacol*. 2018;27:123-134.
6. Periti P, Mazzei T, Mini E, Novelli A. Pharmacokinetic drug interactions of macrolides. *Clin Pharmacokinet*. 1992;23:106-131.
7. Cheung KK, Senior PA. Tacrolimus toxicity in islet transplantation due to interaction with macrolides. *Clin Diabetes Endocrinol*. 2016;2:2.
8. Pea F, Cojutti P, Tursi V, Livi U, Baraldo M. Everolimus overexposure in a heart transplant patient receiving clarithromycin for the treatment of pneumonia. *Transpl Infect Dis*. 2015;17:926-928.

9. Parissis H, Gould K, Dark J. Dangerous drug interactions leading to hemolytic uremic syndrome following lung transplantation. *J Cardiothorac Surg*. 2010;5:70.
10. Page RL, Ruscin JM, Fish D, Lapointe M. Possible interaction between intravenous azithromycin and oral cyclosporine. *Pharmacotherapy*. 2001;21:1436-1443.
11. Ljutic D, Rumboldt Z. Possible interaction between azithromycin and cyclosporin: a case report. *Nephron*. 1995;70:130.
12. Bachmann K, Jauregui L, Chandra R, Thakker K. Influence of a 3-day regimen of azithromycin on the disposition kinetics of cyclosporine A in stable renal transplant patients. *Pharmacol Res*. 2003;47:549-554.
13. Shullo MA, Schonder K, Teuteberg JJ. Elevated tacrolimus levels associated with intravenous azithromycin and ceftriaxone: a case report. *Transplant Proc*. 2010;42:1870-1872.
14. Merck & Co., Inc., Dificid (fidaxomicin), United States prescribing information. Whitehouse Station, NJ, December 2015.
15. Nivoix Y, Levêque D, Herbrecht R, Koffel JC, Beretz L, Ubeaud-Sequier G. The enzymatic basis of drug-drug interactions with systemic triazole antifungals. *Clin Pharmacokinet*. 2008;47:779-792.
16. Brüggemann R, Alffenaar J-W, Blijlevens N, et al. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. *Clin Infect Dis*. 2009;48:1441-1458.
17. Groll AH, Townsend R, Desai A, et al. Drug-drug interactions between triazole antifungal agents used to treat invasive aspergillosis and immunosuppressants metabolized by cytochrome P450 3A4. *Transpl Infect Dis*. 2017;19:e12751.
18. Dodds-Ashley E. Management of drug and food interactions with azole antifungal agents in transplant recipients. *Pharmacotherapy*. 2010;30:842-854.
19. Novartis Pharmaceuticals Corporation. Zortress (everolimus) United States prescribing information. NJ: East Hanover; January 2018.
20. Thomas PP, Manivannan J, John GT, Jacob CK. Sirolimus and ketoconazole co-prescription in renal transplant recipients. *Transplantation*. 2004;77:474-475.
21. Gonzalez F, Espinoza M, Herrera P, et al. Everolimus versus azathioprine in a cyclosporine and ketoconazole-based immunosuppressive therapy in kidney transplant: 3-year follow-up of an open-label, prospective, cohort, comparative clinical trial. *Transplant Proc*. 2010;42:270-272.
22. El-Agroudy AE, Sobh MA, Hamdy AF, Ghoneim MA. A prospective, randomized study of coadministration of ketoconazole and cyclosporine a in kidney transplant recipients: ten-year follow-up. *Transplantation*. 2004;77:1371-1376.
23. El-Dahshan KF, Bakr MA, Donia AF, Badr Ael S, Sobh MA. Ketoconazole-tacrolimus coadministration in kidney transplant recipients: two-year results of a prospective randomized study. *Am J Nephrol*. 2006;26:293-298.
24. Kramer MR, Marshall SE, Denning DW, et al. Cyclosporine and itraconazole interaction in heart and lung transplant recipients. *Ann Intern Med*. 1990;113:327-329.
25. Trenk D, Brett W, Jähnchen E, Birnbaum D. Time course of cyclosporin/itraconazole interaction. *Lancet*. 1987;330:1335-1336.
26. Shitrit D, Ollech JE, Ollech A, et al. Itraconazole prophylaxis in lung transplant recipients receiving tacrolimus (FK 506): efficacy and drug interaction. *J Heart Lung Transplant*. 2005;24:2148-2152.
27. Banerjee R, Leaver N, Lyster H, Banner NR. Coadministration of itraconazole and tacrolimus after thoracic organ transplantation. *Transplant Proc*. 2001;33:1600-1602.
28. Said A, Garnick JJ, Dieterle N, Peres E, Abidi MH, Ibrahim RB. Sirolimus-itraconazole interaction in a hematopoietic stem cell transplant recipient. *Pharmacotherapy*. 2006;26:289-295.
29. Kuypers DR, Claes K, Evenepoel P, et al. Drug interaction between itraconazole and sirolimus in a primary renal allograft recipient. *Transplantation*. 2005;79:737.
30. Sadaba B, Campanero MA, Quetglas EG, Azanza JR. Clinical relevance of sirolimus drug interactions in transplant patients. *Transplant Proc*. 2004;36:3226-3228.
31. Kovarik JM, Hsu CH, McMahon L, Berthier S, Rordorf C. Population pharmacokinetics of everolimus in de novo renal transplant patients: impact of ethnicity and comedications. *Clin Pharmacol Ther*. 2001;70:247-254.
32. Dodds ES, Drew RH, Perfect JR. Antifungal pharmacodynamics: review of the literature and clinical applications. *Pharmacotherapy*. 2000;20:1335-1355.
33. Page RL, Mueller SW, Levi ME, Lindenfeld J. Pharmacokinetic drug-drug interactions between calcineurin inhibitors and proliferation signal inhibitors with anti-microbial agents: implications for therapeutic drug monitoring. *J Heart Lung Transplant*. 2011;30:124-135.
34. Pfizer Incorporated P. VFEND (voriconazole for Injection); VFEND Tablets (voriconazole); VFEND (voriconazole for oral suspension). New York, New York: United States prescribing information; May 2018.
35. Surowiec D, DePestel DD, Carver PL. Concurrent administration of sirolimus and voriconazole: a pilot study assessing safety and approaches to appropriate management. *Pharmacotherapy*. 2008;28:719-729.
36. Billaud Em, Antoine C, Berge M, et al. Management of metabolic cytochrome P450 3A4 drug-drug interaction between everolimus and azole antifungals in a renal transplant patient. *Clin Drug Investig*. 2009;29:481-486.
37. Pea F, Baccarani U, Tavio M, et al. Pharmacokinetic interaction between everolimus and antifungal triazoles in a liver transplant patient. *Ann Pharmacother*. 2008;42:1711-1716.
38. Merck and Co, Inc., Noxafil (posaconazole) oral suspension for oral use, United States prescribing information, Whitehouse Station. NJ, September 2017.
39. Sansone-Parsons A, Krishna G, Martinho M, Kantesaria B, Gelone S, Mant TG. Effect of oral posaconazole on the pharmacokinetics of cyclosporine and tacrolimus. *Pharmacotherapy*. 2007;27:825-834.
40. Moton A, Ma L, Krishna G, Martinho M, Seiberling M, McLeod J. Effects of oral posaconazole on the pharmacokinetics of sirolimus. *Curr Med Res Opin*. 2009;25:701-707.
41. Launay M, Roux A, Beaumont L, et al. Posaconazole tablets in real-life lung transplantation: impact on exposure, drug-drug interactions, and drug management in lung transplant patients, including those with cystic fibrosis. *Antimicrob Agents Chemother*. 2018;62:e02061-e2117.
42. Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. *Pharmacotherapy*. 2006;26:1730-1744.
43. Groll AH, Desai A, Han D, et al. Pharmacokinetic assessment of drug-drug interactions of isavuconazole with the immunosuppressants cyclosporine, mycophenolic acid, prednisolone, sirolimus, and tacrolimus in healthy adults. *Clin Pharmacol Drug Dev*. 2017;6:76-85.
44. Rivosecchi RM, Clancy CJ, Shields RK, et al. Effects of isavuconazole on the plasma concentrations of tacrolimus among solid-organ transplant patients. *Antimicrob Agents Chemother*. 2017;61:e00970-e1017.
45. Kim T, Jancel T, Kumar P, Freeman AF. Drug–drug interaction between isavuconazole and tacrolimus: a case report indicating the need for tacrolimus drug-level monitoring. *J Clin Pharm Ther*. 2015;40:609-611.

46. Vasquez E, Pollak R, Benedetti E. Clotrimazole increases tacrolimus blood levels: a drug interaction in kidney transplant patients. *Clin Transplant*. 2001;15:95-99.
47. Vasquez EM, Shin GP, Sifontis N, Benedetti E. Concomitant clotrimazole therapy more than doubles the relative oral bioavailability of tacrolimus. *Ther Drug Monit*. 2005;27:587-591.
48. Mieles L, Venkataramanan R, Yokoyama I, Warty VJ, Starzl TE. Interaction between FK506 and clotrimazole in a liver transplant recipient. *Transplantation*. 1991;52:1086-1087.
49. Choy M. Tacrolimus interaction with clotrimazole: a concise case report and literature review. *Pharmacotherapy*. 2010;35:568-569.
50. El-Asmar J, Gonzalez R, Bookout R, Mishra A, Kharfan-Dabaja MA. Clotrimazole troches induce supratherapeutic blood levels of sirolimus and tacrolimus in an allogeneic hematopoietic cell-transplant recipient resulting in acute kidney injury. *Hematol Oncol Stem Cell Ther*. 2016;9:157-161.
51. Laub MR, Crow SA. Personett HA, Dierkhising R, Boilson B, Razonable R. Effects of clotrimazole troches on tacrolimus dosing in heart transplant recipients. *Transpl Infect Dis*. 2018;20:e12979.
52. Glynn AM, Slaughter RL, Brass C, D'Ambrosio R, Jusko WJ. Effects of ketoconazole on methylprednisolone pharmacokinetics and cortisol secretion. *Clin Pharmacol Therap*. 1986;39:654-659.
53. Varis T, Kivisto KT, Backman JT, Neuvonen PJ. Itraconazole decreases the clearance and enhances the effects of intravenously administered methylprednisolone in healthy volunteers. *Pharmacol Toxicol*. 1999;85:29-32.
54. Kandrotas RJ, Slaughter RL, Brass C, Jusko WJ. Ketoconazole effects on methylprednisolone disposition and their joint suppression of endogenous cortisol. *Clin Pharmacol Therap*. 1987;42:465-470.
55. Yamashita SK, Ludwig EA, Middleton E Jr, Jusko WJ. Lack of pharmacokinetic and pharmacodynamic interactions between ketoconazole and prednisolone. *Clin Pharmacol Ther*. 1991;49:558-570.
56. Ludwig EA, Slaughter RL, Savliwala M, et al. Steroid-specific effects of ketoconazole on corticosteroid disposition: Unaltered prednisolone elimination. *DICP*. 1989;23:858-861.
57. Jeng S, Chanchairujira T, Jusko W, Steiner R. Prednisone metabolism in recipients of kidney or liver transplants and in lung recipients receiving ketoconazole. *Transplantation*. 2003;75:792-795.
58. Lebrun-Vignes B, Archer VC, Diquet B, et al. Effect of itraconazole on the pharmacokinetics of prednisolone and methylprednisolone and cortisol secretion in healthy subjects. *Br J Clin Pharmacol*. 2001;51:443-450.
59. Varis T, Kivisto KT, Neuvonen PJ. The effect of itraconazole on the pharmacokinetics and pharmacodynamics of oral prednisolone. *Eur J Clin Pharmacol*. 2000;56:57-60.
60. Stock PG, Barin B, Murphy B, et al. Outcomes of kidney transplantation in HIV-infected recipients. *N Engl J Med*. 2010;363:2004-2014.
61. Shaffer AA, Durand CM. Solid organ transplantation for HIV-infected individuals. *Curr Treat Options Infect Dis*. 2018;10:107-120.
62. Frassetto La, Browne M, Cheng A, et al. Immunosuppressant pharmacokinetics and dosing modifications in HIV-1 infected liver and kidney transplant recipients. *Am J Transplant*. 2007;7:2816-2820.
63. Primeggia J, Trimpone JG Jr, Kumar PN. Pharmacologic issues of antiretroviral agents and immunosuppressive regimens in HIV-infected solid organ transplant recipients. *Infect Dis Clin North Am*. 2013;27:473-486.
64. van Maarseveen EM, PharmD, Rogers CC, Trofe-Clark J, van Zuilen AD, Mudrikova T. Drug–drug interactions between antiretroviral and immunosuppressive agents in HIV-infected patients after solid organ transplantation: a review. *AIDS Patient Care STDs*. 2012;26:568-581.
65. Gilead Sciences, Inc.Stribilid (cobicistat), United States Prescribing Information. Foster City, CA, Aug 2017
66. Patel SJ, Kuten SA, Musick WL, Gaber AO, Monsour HP, Knight RJ. Combination drug products for HIV - a word of caution for the transplant clinician. *Am J Transplant*. 2016;16:2479-2482.
67. Han Z, Kane BM, Petty LA, Josephson MA, Sutor J, Pursell KJ. Cobicistat significantly increases tacrolimus serum concentrations in a renal transplant recipient with human immunodeficiency virus infection. *Pharmacotherapy*. 2016;36:e50-e53.
68. Sawinski D, Shelton Ba, Mehta S, et al. Impact of Protease Inhibitor-Based Anti-Retroviral Therapy on Outcomes for HIV+ Kidney Transplant Recipients. *Am J Transplant*. 2017;17:3114-3122.
69. Bickel M, Anadol E, Vogel M, et al. Daily dosing of tacrolimus in patients treated with HIV-1 therapy containing a ritonavir-boosted protease inhibitor or raltegravir. *J Antimicrob Chemother*. 2010;65:999-1004.
70. Tricot L, Teicher E, Peytavin G, et al. Safety and efficacy of raltegravir in HIV-infected transplant patients co-treated with immunosuppressive drugs. *Am J Transplant*. 2009;9:1946-1952.
71. Moreno A, Pérez-Elías MJ, Casado JL, et al. Raltegravir-based highly active antiretroviral therapy has beneficial effects on the renal function of human immunodeficiency virus-infected patients after solid organ transplantation. *Liver Transpl*. 2010;16:530-532.
72. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. *N Engl J Med*. 2017;377:2433-2444.
73. Merck and Co Inc.Prevymis (letermovir) tablets for oral use, Prevymis (letermovir) injection for intravenous use, United States prescribing information. Whitehouse Station, NJ, November 2017.
74. AASLD-IDSA. Patients Who Develop Recurrent HCV Infection Post Liver Transplantation. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed July 8, 2018
75. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol*. 2017;66(1):153–194.
76. Forns X, Berenguer M, Herzer K, et al. Efficacy, safety, and pharmacokinetics of simeprevir, daclatasvir, and ribavirin in patients with recurrent hepatitis C virus genotype 1b infection after orthotopic liver transplantation: The Phase II SATURN study. *Transpl Infect Dis*. 2017;19(3):e12696.
77. Ouwerkerk-Mahadevan S, Snoeys J, Peeters M, Beumont-Mauviel M, Simion A. Drug-drug interactions with the NS3/4A protease inhibitor simeprevir. *Clin Pharmacokinet*. 2016;55:197-208.
78. Kwok RM, Ahn J, Schiano TD, et al. Sofosbuvir plus ledispasvir for recurrent hepatitis C in liver transplant recipients. *Liver Transpl*. 2016;22:1536-1543.
79. Antonini TM, Coilly A, Rossignol E, et al. Sofosbuvir-based regimens in HIV/HCV coinfected patients after liver transplantation: results from the ANRS CO23 CUPILT study. *Transplantation*. 2018;102:119-126.
80. Ha YE, Joo EJ, Park SY, et al. Tacrolimus as a risk factor for tuberculosis and outcome of treatment with rifampicin in solid organ transplant recipients. *Transpl Infect Dis*. 2012;14:626-634.
81. Manitpisitkul W, McCann E, Lee S, Weir MR. Drug interactions in transplant patients: what everyone should know. *Curr Opin Nephrol Hypertens*. 2009;18:404-411.
82. Lopez-Montes A, Gallego E, Lopez E, et al. Treatment of tuberculosis with rifabutin in a renal transplant recipient. *Am J Kidney Dis*. 2004;44:e59-63.
83. Chenhsu RY, Loong CC, Chou MH, Lin MF, Yang WC. Renal allograft dysfunction associated with rifampin-tacrolimus interaction. *Ann Pharmacother*. 2000;34:27-31.
84. Modry DL, Stinson EB, Oyer PE, Jamieson SW, Baldwin JC, Shumway NE. Acute rejection and massive cyclosporine requirements in heart transplant recipients treated with rifampin. *Transplantation*. 1985;39:313-314.

85. Kovarik JM, Hartmann S, Figueiredo J, Rouilly M, Port A, Rordorf C. Effect of rifampin on apparent clearance of everolimus. *Ann Pharmacother*. 2002;36:981-985.
86. Ngo BT, Pascoe M, Khan D. Drug interaction between rifampicin and sirolimus in transplant patients. *Saudi J Kidney Dis Transpl*. 2011;22:112-115.
87. Bhaloo S, Prasad GV. Severe reduction in tacrolimus levels with rifampin despite multiple cytochrome P450 inhibitors: a case report. *Transplant Proc*. 2003;35:2449-2451.
88. Crabol Y, Catherinot E, Veziris N, Jullien V, Lortholary O. Rifabutin: where do we stand in 2016? *J Antimicrob Chemother*. 2016;71:1759-1771.
89. Hickey MD, Quan DJ, Chin-Hong PV, Roberts JP. Use of rifabutin for the treatment of a latent tuberculosis infection in a patient after solid organ transplantation. *Liver Transpl*. 2013;19:457-461.
90. Naesens M, Kuypers D, Streit F, et al. Rifampin induces alterations in mycophenolic acid glucuronidation and elimination: implications for drug exposure in renal allograft recipients. *Clin Pharmacol Ther*. 2006;80:509-521.
91. Genetech USA, Inc., Mycophenolate mofetil (CellCept) capsules, tablets and oral suspension and mycophenolate mofetil hydrochloride for injection, United States prescribing information. South San Francisco, CA, July 2015.
92. Carrie F, Roblot P, Bouquet S, et al. Rifampin-induced nonresponsiveness of giant cell arteritis to prednisone treatment. *Arch Intern Med*. 1994;154:1521-1524.
93. Bristol-Myers Squibb Company. Sustiva (efavirenz) United States prescribing information. Princeton NJ, October 2017.
94. Teicher E, Vincent I, Bonhomme-Faivre L, et al. Effect of highly active antiretroviral therapy on tacrolimus pharmacokinetics in hepatitis C virus and HIV co-infected liver transplant recipients in the ANRS HC-08 study. *Clin Pharmacokinet*. 2007;46:941-952.
95. Durante-Mangoni E, Maiello C, Limongelli G, et al. Management of immunosuppression and antiviral treatment before and after heart transplant for HIV-associated dilated cardiomyopathy. *Int J Immunopathol Pharmacol*. 2014;27:113-120.
96. Bristol-Myers Squibb Company. Belatacept (Nulojix), United States prescribing information. Princeton; NJ, September 2014.
97. Termeer A, Hoitsma AJ, Koene RA. Severe nephrotoxicity caused by the combined use of gentamicin and cyclosporine in renal allograft recipients. *Transplantation*. 1986;42(220):95-98.
98. Hows JM, Chipping PM, Fairhead S, et al. Nephrotoxicity in bone marrow transplant recipients treated with cyclosporine A. *Br J Haematol*. 1983;54:69-78.
99. Kennedy MS, Deeg HJ, Siegel M, et al. Acute renal toxicity with combined use of amphotericin B and cyclosporine after marrow transplantation. *Transplantation*. 1983;35:211-215.
100. Zafrani L, Truffaut L, Kreis H, et al. Incidence, risk factors and clinical consequences of neutropenia following kidney transplantation: a retrospective study. *Am J Transplant*. 2009;9:1816-1825.
101. Brennan DC, Daller JA, Lake KD, Cibrik D, Del Castillo D. Thymoglobulin Induction Study Group. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med*. 2006;355:1967-1977.
102. Hanaway MJ, Woodle ES, Mulgaonkar S, et al. Alemtuzumab induction in renal transplantation. *N Engl J Med*. 2011;19:1909-1919.
103. Nashan B, Gaston R, Emery V, et al. Review of cytomegalovirus infection findings with mammalian target of rapamycin inhibitor-based immunosuppressive therapy in de novo renal transplant recipients. *Transplantation*. 2012;93:1075-1085.
104. Husain S, Singh N. The impact of novel immunosuppressive agents on infections in organ transplant recipients and the interactions of these agents with antimicrobials. *Clin Infect Dis*. 2002;35:53-61.
105. Neff RT, Jindal RM, Yoo DY, Hurst FP, Agodoa LY, Abbott KC. Analysis of USRDS: incidence and risk factors for Pneumocystis jiroveci pneumonia. *Transplantation*. 2009;88:135-141.
106. Margolis DM, Kewn S, Coull JJ, et al. The addition of mycophenolate mofetil to antiretroviral therapy including abacavir is associated with depletion of intracellular deoxyguanosine triphosphate and a decrease in plasma HIV-1 RNA. *J Acquir Immune Defic Syndr*. 2002;31:45-49.

How to cite this article: Sparkes T, Lemonovich TL. Interactions between anti-infective agents and immunosuppressants—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant*. 2019;33:e13510. https://doi.org/10.1111/ctr.13510