INTERACTIONS BETWEEN AZOLE ANTIFUNGALS AND ANTIRETROVIRALS

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
Kinetic Characteristics	Substrate of CYP3A4 (11%)[1], p-glycoprotein[2]. Inhibits CYP3A4, 2C9[3], 2C19[3], UGT[4, 5]	Substrate of CYP3A4[6], p-glycoprotein[2]. Inhibits CYP3A4[6], p-glycoprotein[2].	Substrate of CYP3A4. Inhibits CYP3A4 (potent), 2C9, 1A2, p-glycoprotein[7], UGT.[4, 5]	Substrate of p-glycoprotein, UGT1A4. Inhibits CYP3A4, p-glycoprotein.	Inhibits CYP3A4. Induces CYP3A, 2B (preliminary data in animal studies).	Substrate of CYP2C19 (major), CYP3A4, CYP2C9. Inhibits CYP3A4[8], 2C9, 2C19.
CCR5 Inhibitor						
Maraviroc (metabolized by CYP3A4 and p-glycoprotein.[9])	Potential for fluconazole to ↑ maraviroc concentrations via CYP3A4 inhibition. Administration of the standard maraviroc dose (300 mg BID) should be done with caution.[9]	Potential for itraconazole to ↑ maraviroc concentrations via CYP3A4 inhibition. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[9]	When given with ketoconazole 400 mg QD, maraviroc AUC ↑ 5-fold, Cmax ↑ 3.4-fold.[10] Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[9]	Potential for posaconazole to ↑ maraviroc concentrations via CYP3A4 inhibition. Reduction of maraviroc dose by 50% in the presence of protease inhibitors/potent CYP3A4 inhibitors is recommended.[9]		Potential for ↑ maraviroc concentrations due to CYP3A4 inhibition by voriconazole. Since voriconazole is considered a moderate CYP3A4 inhibitor, the magnitude of the interaction is likely less than with more potent inhibitors. Monitor closely for maraviroc-related toxicity if maraviroc 300mg twice daily dose is used.[9] It is unclear whether a dosage ↓of maraviroc to 150 mg twice daily is recommended as it is with other more potent CYP3A4 inhibitors (i.e. ketonazole, itraconazole, clarithromycin).[9]
Integrase Inhibitor						
Dolutegravir (metabolized by UGT1A1 with some contribution by CYP3A4. Inhibits renal OCT2 transporter; no other inhibitory or	Interactions are unlikely based on dolutegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on dolutegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on dolutegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on dolutegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on dolutegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on dolutegravir metabolism. Use standard doses of both drugs.

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inductive potential in vitro.[11])						
Elvitegravir (metabolized by CYP3A4, UGT1A1/3, moderate 2C9 inducer) Boosted by cobicistat (3A4, 2D6 substrate, inhibitor of 3A4, 2D6, P-glycoprotein)	Potential for ↑ fluconazole and/or elvitegravir and cobicistat concentrations.	Potential for ↑ itraconazole and/or elvitegravir and cobicistat concentrations. Do not exceed maximum daily dose of itraconazole 200 mg[12]	In a healthy volunteer study, subjects received elvitegravir 150/ritonavir 100 mg daily alone and then with ketoconazole 200 mg BID, each for 10 days, followed by 4 more days of ketoconazole 200 mg BID alone. In the presence of ketoconazole, modest increases in elvitegravir exposures were observed: 17% ↑ Cmax, 48% ↑ AUC, 67% ↑Cmin. A maximum ketoconazole dose of 200 mg once daily is recommended when coadministering with boosted elvitegravir.[13]	Potential for ↑ posaconazole and/or elvitegravir and cobicistat concentrations.	Potential for ↑ ravuconazole and/or ↑/↓ elvitegravir and cobicistat concentrations.	Potential for ↑ voriconazole and/or elvitegravir and cobicistat concentrations.[12]
Raltegravir (metabolized by UGT1A1 and has no inhibitory or inductive potential in vitro.[14])	Interactions are unlikely based on raltegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on raltegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on raltegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on raltegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on raltegravir metabolism. Use standard doses of both drugs.	Interactions are unlikely based on raltegravir metabolism. Use standard doses of both drugs.
NNRTIs						
Delavirdine (metabolized via CYP3A4; also inhibits 3A4, as well as 2C9, 2C19.[15])	A dual inhibition interaction is possible via CYP 3A4 inhibition by delavirdine and fluconazole. No interaction noted.[16] Use standard doses of both drugs.	A dual inhibition interaction is possible via CYP 3A4 inhibition by delavirdine and itraconazole. Monitor for both delavirdine and itraconazole toxicity (i.e. hepatotoxicity).	A dual inhibition interaction is possible via CYP 3A4 inhibition by delavirdine and ketoconazole. No delavirdine dosage adjustment recommended with inhibitors of CYP3A4 or CYP2D6.[16] Monitor for both delavirdine and ketoconazole	Possible ↑ delavirdine concentrations due to CYP3A4 inhibition by posaconazole. Monitor for delavirdine toxicity.		

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
			toxicity (i.e. hepatotoxicity).			
Efavirenz (In vitro is a potent inducer and inhibitor of CYP3A4. Induces 2B6.[17] Also inhibits CYP2C9, 2C19.[3])	Potential for dual induction/inhibition interaction due to efavirenz-mediated CYP3A4 induction and fluconazole-related CYP3A4 inhibition. No interaction noted with combination.[18] Use standard doses of both drugs.	In a pharmacokinetic study of healthy subjects, efavirenz 600 mg plus itraconazole 200 mg BID for 14 days led to a 39% ↓ AUC of itraconazole and 37% ↓ AUC of its hydroxyl-metabolite; EFV exposures were not affected.[19] Case report of HIV-positive male with disseminated histoplasmosis with undetectable itraconazole concentrations and persistently elevated urinary *Histoplasma* antigen levels while on efavirenz and itraconazole 200 mg BID. Therapeutic itraconazole levels and a decrease in urinary Histoplasma antigen levels were observed after efavirenz was replaced with atazanavir/ritonavir.[20] In a retrospective cohort analysis, itraconazole levels were assessed in 10 HIV-positive patients with disseminated histoplasmosis; 4 patients were on PI	In a pharmacokinetic study of 12 HIV-infected patients, the kinetics of single-dose ketoconazole 400 mg was measured alone and after 14 days of efavirenz/3TC/d4T. In the presence of steady-state efavirenz, ketoconazole Cmax ↓ 44% and AUC ↓ 72%.[23] Avoid concomitant use; consider alternate antiretroviral or antifungal therapy.	Posaconazole AUC ↓ 50% by efavirenz,[24, 25] likely via efavirenz-mediated induction of posaconazole glucuronidation. **Avoid combination** unless the benefits clearly outweigh the risks of antifungal failure. Consider posaconazole TDM to dose-adjust.[22]		Dual induction/inhibition interaction likely due to efavirenz-mediated CYP3A4, 2C9, 2C19 induction of voriconazole and voriconazole-related CYP3A4 inhibition of efavirenz metabolism. 80% ↓ voriconazole AUC; 43% ↑ efavirenz AUC when given as **voriconazole 400 mg every 12 hours (day 1), then 200 mg every 12 hours and efavirenz 400 mg daily** x 9 days.[26] 55% ↓ voriconazole AUC; 1% ↑ efavirenz AUC when given as voriconazole 300 mg every 12 hours and efavirenz 300 mg daily.[27] 7% ↓ voriconazole AUC; 17% ↑ efavirenz AUC when given as **voriconazole 400 mg every 12 hours and efavirenz 300 mg daily**. These values are similar to monotherapy with either agent alone.[27] Case report in 40 year-old male with mild HCV-related cirrhosis and cryptococcal

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
		therapy, 4 on NNRTIs, and 2 on both PIs and NNRTI therapy. All NNRTI patients had undetectable itraconazole concentrations, vs.1/4 PI patients. Two patients who switched from NNRTI to PI therapy subsequently had therapeutic itraconazole levels.[21] No data using higher doses of itraconazole. **Avoid this combination if possible.** If coadministered, closely monitor itraconazole concentration and adjust dose accordingly.[22] Use of alternate antifungal treatment may be necessary or replacement of efavirenz with a non-inducing class of antiretrovirals such as protease inhibitors, integrase or CCR5 inhibitors if possible.				meningitis requiring a dosage adjustment of oral voriconazole titrated to **200 mg twice daily and efavirenz 300mg once daily** to yield therapeutic concentrations of both drugs and positive clinical outcomes.[28] **Contraindicated** at standard doses.[18] Recommended dosage adjustment: ↑ voriconazole maintenance dose to 400 mg twice daily (from 200mg twice daily) and ↓ efavirenz dose to 300mg once daily (from 600mg once daily). Use the capsule formulation to obtain this dose since efavirenz 600mg tablets should not be broken.[18] Short-term co-administration (i.e. a few days) may not require empiric dosage adjustments. When either agent is discontinued, dosage readjustments are required.
Etravirine (substrate of CYP3A4, CYP2C9, and CYP2C19. Weak inducer of CYP3A4, weak	In healthy volunteers, coadministration of etravirine 200 mg BID plus fluconazole 200 mg daily for 9 days resulted in 109% ↑ Cmin, 75% ↑ Cmax	Possible ↑ etravirine concentrations and/or ↓ concentrations of itraconazole. Dose adjustments for itraconazole may be necessary.[22, 29]	Possible ↑ etravirine plasma concentrations and/or ↓ plasma concentrations of ketoconazole.[29] Dose adjustments for	Possible ↑ etravirine concentrations due to CYP3A4 inhibition by posaconazole.[29] No anticipated effect on posaconazole concentrations.		In healthy volunteers, coadministration of etravirine 200 mg BID plus voriconazole 200 mg BID for 9 days resulted in 52% ↑ Cmin, 26% ↑ Cmax

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
inhibitor of CYP2C9 and a moderate inhibitor of CYP2C19. Also inhibits p-glycoprotein. No clinically relevant effect on CYP1A2 or CYP2D6.[29, 30])	and 86% ↑ AUC of etravirine, while fluconazole parameters were unchanged compared to either drug administered alone. The combination was well tolerated.[31] Use standard doses of both drugs. Monitor for side effects of etravirine.	Consider TDM of both drugs if possible.	ketoconazole may be necessary. Monitor for ketoconazole efficacy.	Monitor for etravirine-related toxicity.		and 36% ↑ AUC of etravirine, and 23% ↑ Cmin and 14% ↑ AUC of voriconazole (although no ↑ was observed in carriers of CYP2C19*2 allele) compared to either drug administered alone. The combination was well tolerated.[31] Dose adjustments are not required. Monitor closely for toxicity. ***see also entry for darunavir/ritonavir plus etravirine plus voriconazole***
Nevirapine (substrate and potent inducer of CYP3A4 and 2B6 enzymes.[2])	In a study of 24 HIV+ subjects, combination of nevirapine 200 mg BID and fluconazole 200 mg daily resulted in ~100% ↑ AUC of nevirapine compared with historical data; 25% of subjects also developed elevated liver transaminases >5 times upper limit of normal. Nevirapine did not affect the pharmacokinetics of fluconazole.[32] In a retrospective study of 122 HIV-infected patients receiving nevirapine, those also taking fluconazole 200 or 400 mg daily (n=41) had NVP Cmin 76% higher compared to those not taking fluconazole. One	In a healthy volunteer, cross-over study of itraconazole 200 mg QD, nevirapine 200 mg QD or the combination (each for 7 days), itraconazole Cmax ↓ 38% and AUC ↓ 61% in the presence of nevirapine. Nevirapine parameters were not changed.[35] **Avoid combination if possible.** If coadministered, monitor itraconazole concentration and adjust dose accordingly.[22]	Ketoconazole levels sig. reduced (63% ↓ AUC, 40% ↓ Cmax,) 15-20% ↑ NVP concentrations.[36] Avoid concomitant use; consider alternate antiretroviral or antifungal therapy.	Possible ↑ nevirapine concentrations due to CYP3A4 inhibition by posaconazole. No anticipated effect on posaconazole concentrations. Monitor for nevirapine-related toxicity.		Potential ↓ voriconazole AUC and ↑ nevirapine AUC. Avoid combination if possible. If using the combination, consider TDM of both agents to dose-adjust. Monitor for nevirapine toxicity and voriconazole efficacy.

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
	patient on fluconazole developed clinical hepatitis.[33] In a prospective placebo-controlled trial, low-dose fluconazole (200mg 3x/weekly) resulted in a 29% ↑ AUC of nevirapine. There was no additional risk of hepatotoxicity with the combination.[34] Use combination with caution. Monitor closely for nevirapine associated adverse effects including hepatotoxicity.					
Rilpivirine (metabolized primarily by CYP3A4, as well as CYP2C19, 1A2, 2C8/9/10 (minor). Moderate inducer of CYP2C19, slight inducer of CYP1A2, 2B6 and 3A4. A clinically relevant effect on CY3A activity is considered unlikely with phase III dose.[37] No effect on CYP2E1 activity.[38])	Fluconazole is the preferred azole option for patients taking rilpivirine. Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[39].	Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[22, 39]	In healthy subjects, steady-state coadministration of rilpivirine 150 mg QD plus ketoconazole 400 mg QD, rilpivirine AUC ↑ 49%, Cmax ↑ 30% and Cmin ↑ 76%, while ketoconazole AUC ↓ 24%, Cmax ↓ 15% and Cmin ↓ 66% compared to each agent alone.[40] No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[39]	Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[39]		Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.[39]
PIs						
Atazanavir (Primarily metabolized by CYP3A4; also	In healthy subjects, coadministration of atazanavir 300/rtv 100 mg QD plus fluconazole 200 mg	Potential for ↑ concentrations of PIs and/or itraconazole via CYP 3A4 inhibition by both agents.	In a healthy volunteer study, coadministration of 400 mg atazanavir plus 200 mg	Atazanavir: 268% ↑ AUC atazanavir when given as 300 mg daily x 14 days with posaconazole 400 mg		Paradoxical interaction displaying short-term inhibition followed by induction at steady-state.

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
inhibits CYP3A and UGT1A1.[41] Atazanavir alone does not induce glucuronidation, while atazanavir/ ritonavir does induce glucuronidation.[42])	QD for 10 days did not result in changes to pharmacokinetic parameters of either ATV, rtv or fluconazole.[43] Use standard doses of both drugs.	Clinical significance unclear, monitor for dose-related toxicities.	ketoconazole daily did not result in significant changes in atazanavir concentrations.[44] Dosage adjustment not necessary with unboosted atazanavir.	twice daily x 7 days Atazanavir/RTV: 146% ↑ AUC atazanavir when given as 300 mg/100 mg daily x 14 days with posaconazole 400 mg twice daily x 7 days.[24, 25] Empiric dosage adjustments are not recommended. Monitor for atazanavir-related toxicity. In cases of suspected toxicity, TDM may be useful to dose-adjust.		• Short-term: ↑ voriconazole concentrations initially due to RTV-related CYP3A4 inhibition, particularly in CYP2C19 poor metabolizers. • Steady-state: ↓ voriconazole concentrations due to CYP2C19/2C9 induction. With RTV 100 mg twice daily: 39% ↓ voriconazole AUC; 14% ↓ RTV AUC[45, 46] Use of low boosting doses of RTV (i.e. 100mg twice daily) combined with any of the other PIs should be **avoided** unless the benefits outweigh the risks of antifungal failure.[41, 46] Case report of positive immunologic and virologic response in a patient with multidrug-resistant HIV on **atazanavir 300 mg QD,** raltegravir 400 mg BID and tenofovir/emtricitabine concurrently with **voriconazole 200 mg twice daily**.[47]

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
						An open-label nonrandomized study assessed the impact of atazanavir/ritonavir 300/100-mg QD on the kinetics of voriconazole in CYP2C19 extensive metabolizers (EMs) and poor metabolizers (PMs). Among EMs, coadministration resulted in 33% ↓ AUC and ↓ 39% Cmin of voriconazole, and 12% ↓ AUC and 20% ↓ Cmin of atazanavir. Among PMs, coadministration resulted in ↑ voriconazole Cmax, AUC and Cmin by 4.4-, 5.6-, and 7.7-fold, while atazanavir AUC ↓ 20%, Cmax ↓ 19% and Cmin ↓ 31%. Ritonavir AUC and Cmax did not change substantially with voriconazole codosing in either study group.[48] Complex case report of a female with CYP2C19*17 allele (rapid metabolizer) who achieved target Cmin voriconazole concentrations with concomitant raltegravir and TDF/FTC and esomeprazole

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
						(CYP2C19 inhibitor). The patient was switched to unboosted atazanavir with ranitidine and the esomeprazole was stopped.CYP3A4 inhibition by atazanavir coupled with uninhibited CYP2C19 resulted in subtherapeutic voriconazole Cmin. Management involved replacement with darunavir/ritonavir and reintroduction of esomprazole (double blockade of CYP3A4 and 2C19 pathways). The voriconazole Cmin ↑14-fold and dose was reduced by 50%.[49] **Avoid combination** unless the benefits outweigh the risks of antifungal failure.
Darunavir (Primarily metabolized by CYP3A4. Inhibits CYP3A4.[50])	Potential for ↑ concentrations of PIs and/or fluconazole via CYP 3A4 inhibition by both agents. Monitor for both PI and fluconazole toxicity (i.e. hepatotoxicity).	Coadministration of darunavir 400/100 mg BID and ketoconazole 200 mg BID led to 212% ↑ ketoconazole exposure and 42% ↑ darunavir exposure.[51] A similar interaction may be possible with itraconazole. Do not exceed 200 mg itraconazole per day while on darunavir/ritonavir.	Coadministration of darunavir 400 mg BID and ketoconazole 200 mg BID in healthy volunteers (n=6) led to 155% ↑ AUC, 179% ↑ Cmin of darunavir, and no significant change in ketoconazole levels. Coadministration of darunavir 400/100 mg BID and ketoconazole 200 mg BID in healthy volunteers (n=17) led to 212% ↑	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.		Paradoxical interaction displaying short-term inhibition followed by induction at steady-state. • Short-term: ↑ voriconazole concentrations initially due to RTV-related CYP3A4 inhibition, particularly in CYP2C19 poor metabolizers. • Steady-state: ↓ voriconazole

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
			ketoconazole exposure and 42% ↑ darunavir exposure.[51] Do not exceed 200 mg ketoconazole per day while on darunavir/ritonavir.			concentrations due to CYP2C19/2C9 induction. <u>With RTV 100 mg twice daily:</u> 39% ↓ voriconazole AUC; 14% ↓ RTV AUC[45, 46] Use of low boosting doses of RTV (i.e. 100mg twice daily) combined with any of the other PIs should be **avoided** unless the benefits outweigh the risks of antifungal failure.[46, 50] Consider voriconazole TDM or use other antifungals that do not interact significantly with RTV.
Darunavir/r plus etravirine						Case report of a patient on darunavir 900/100 mg QD, etravirine 200 mg BID, 2 NRTIs and voriconazole 400 mg BID for 6 weeks. Drug levels were obtained during voriconazole co-administration and 3 weeks after voriconazole discontinuation. Therapeutic voriconazole levels were achieved, while etravirine Ctrough ↑ 134%, ritonavir Ctrough was undetectable and darunavir Ctrough

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
						was well below historical reference data. After voriconazole was discontinued, ritonavir Ctrough increased to the same range as the historical control and darunavir Ctrough increased by four-fold. The combination of etravirine/darunavir/ritonavir with voriconazole should be undertaken with caution and BID dosing of darunavir/ritonavir should be considered in this setting. Therapeutic drug monitoring should be utilized when available.[52]
Fosamprenavir (Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir)[53]; also induces CYP3A4[54].)	Potential for ↑ concentrations of PIs and/or fluconazole via CYP 3A4 inhibition by both agents. Monitor for both PI and fluconazole toxicity (i.e. hepatotoxicity).	Potential for ↑ concentrations of PIs and/or itraconazole via CYP 3A4 inhibition by both agents. Clinical significance unclear, monitor for dose-related toxicities.	32% ↑ amprenavir AUC, 44% ↑ ketoconazole AUC.[55] Clinical significance unclear. Monitor for ketoconazole-related toxicities (e.g., hepatotoxicity).	In a 3 period, cross-over, open-label multi-dose study, healthy volunteers received either posaconazole 400 mg BID, fosamprenavir 700/ritonavir 100 mg BID, or posaconazole plus fosamprenavir 700 mg BID for 10 days separated by 17 day washout periods. When posaconazole and fosamprenavir were coadministered, posaconazole AUC ↓ 23% and Cmax ↓ 21% vs. posaconazole alone, and amprenavir AUC ↓ 65% and Cmax ↓		A dual inhibition interaction is possible via CYP 3A4 inhibition by unboosted PI and voriconazole. CYP2C19 poor metabolizers may be at increased risk of higher voriconazole concentrations due to preferential CYP3A4 inhibition. Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity. Consider TDM of both drugs.

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
				36% compared to fosamprenavir-ritonavir. Avoid posaconazole and unboosted fosamprenavir; optimal dosing of posaconazole and boosted fosamprenavir has not yet been determined. If concomitant therapy is required, use boosted fosamprenavir and consider TDM of both fosamprenavir and posaconazole.[56]		
Indinavir (Primarily metabolized by CYP3A4. Inhibitor of CYP3A4; may also be weak inhibitor of CYP2D6.[57, 58])	No clinically significant effect on indinavir AUC.[58] Use standard doses of both drugs.	In a multiple-dose study, administration of itraconazole 200 mg BID with indinavir 600 mg every 8 hours resulted indinavir AUC similar to what would be expected from indinavir 800 mg every eight hours alone.[58] Consider reducing unboosted indinavir dose to 600 mg q8h.	Single-dose study of indinavir 400 mg and ketoconazole 400 mg: 68% ↑ indinavir AUC.[58] If using unboosted indinavir, reduce indinavir dose to 600 mg q8h.	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.		No significant interaction with indinavir.[59] Effects with RTV-boosting unknown. Unboosted indinavir can be co-administered with voriconazole at the usual doses. Caution if using ritonavir-boosted PIs since voriconazole concentrations may ↓ (see ritonavir recommendations).
Lopinavir/ritonavir (Primarily metabolized by CYP3A4. Kaletra inhibits CYP3A4, 2D6 (to lesser extent). Induces glucuronyl transferases and possibly CYP1A2, CYP2C19 and	Clinically significant interaction not expected.[61] Use standard doses of both drugs.	In a case report of an HIV-positive patient on itraconazole 200 mg QD and lopinavir/r, itraconazole levels were significantly ↑ (similar to itraconazole 400 mg QD alone) and hydroxy-itraconazole levels were	Single 200 mg ketoconazole dose had no significant effect on lopinavir/r concentrations.[61] Lopinavir/r AUC increased 3-fold. Ketoconazole doses >200 mg/day not recommended. Monitor for dose-related toxicities.	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.		Paradoxical interaction displaying short-term inhibition followed by induction at steady-state. • Short-term: ↑ voriconazole concentrations initially due to RTV-related CYP3A4 inhibition,

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
2C9.[60])		significantly ↓. Lopinavir/r levels not affected.[62] Similarly, in another case report of an HIV-positive patient with disseminated histoplasmosis infection, lopinavir concentrations remained stable after initiation of itraconazole 200 mg daily, and therapeutic antifungal levels (itraconazole + hydroxy-itraconazole) were achieved along with clinical response.[63] Itraconazole doses >200 mg/day not recommended.[61]				particularly in CYP2C19 poor metabolizers. • <u>Steady-state:</u> ↓ voriconazole concentrations due to CYP2C19/2C9 induction. <u>With RTV 100 mg twice daily:</u> 39% ↓ voriconazole AUC; 14% ↓ RTV AUC[45, 46] Use of low boosting doses of RTV (i.e. 100mg twice daily) combined with any of the other PIs should be **avoided** unless the benefits outweigh the risks of antifungal failure.[46, 61] Consider voriconazole TDM or use other antifungals that do not interact significantly with RTV.
Nelfinavir (Metabolized by CYP3A4 and CYP2C19. Inhibitor of CYP3A4.[64, 65] Induces CYP2B6, 2C8 and 2C9.[66])	Potential for ↑ concentrations of PIs and/or fluconazole via CYP 3A4 inhibition by both agents. Nelfinavir may be administered with azoles including fluconazole, itraconazole and ketoconazole without dosage adjustment.[67]	Potential for ↑ concentrations of PIs and/or itraconazole via CYP 3A4 inhibition by both agents. Clinical significance unclear, monitor for dose-related toxicities.	35% ↑ NFV AUC.[68] Use standard doses of both drugs.	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.	Ravuconazole may exhibit CYP 3A4 inhibitory effects on nelfinavir after a single dose and induction effects of CYP3A and 2B after multiple dosing. 32% ↑ AUC nelfinavir (day 2) and 16% ↓AUC nelfinavir (day 29) after ravuconazole 400 mg daily and nelfinavir 750 mg given as two single doses.[69] Use standard doses of both drugs.	A dual inhibition interaction is possible via CYP 3A4 inhibition by unboosted PI and voriconazole. CYP2C19 poor metabolizers may be at increased risk of higher voriconazole concentrations due to preferential CYP3A4 inhibition. Potential for ↑ concentrations of unboosted PIs and voriconazole. Monitor for both PI and voriconazole toxicity.

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
						Consider TDM of both drugs.
Ritonavir (Potent inhibitor of CYP enzymes in following order: 3A>2D6>2C9, 2C19>>2A6, 2E1. Induces glucuronyl transferases, CYP1A2, CYP2B6, CYP2C9 and CYP2C19.[70])	12% ↑ RTV AUC. Clinical significance unclear.[71] Use standard doses of both drugs.	In a case report, itraconazole blood levels in a patient taking ritonavir and saquinavir showed more than five-fold ↑ increase half-life, and therapeutic levels of itraconazole were still detectable even 27 days after discontinuation of the drug.[72] Use combination with caution and monitor for itraconazole-related toxicities (e.g., hepatotoxicity).	Coadministration of ketoconazole 200 mg daily ritonavir 500 mg BID (n=12) resulted in an 18% ↑ ritonavir AUC, and 3.4 fold ↑ ketoconazole AUC and 55% ↑ Cmax.[71] Ketoconazole doses >200 mg/day not recommended. Monitor for dose-related toxicities.	80% ↑ AUC RTV with RTV 100mg daily x 14 days and posaconazole 400mg twice daily x 7 days.[25] RTV 600mg twice daily had no significant effect on posaconazole concentrations.[73] When ritonavir is used in lower boosting doses of 100mg twice daily, empiric dosage adjustments are likely not required. However if used in larger doses, a ↓ in ritonavir dose may be warranted. Monitor for ritonavir-related toxicity. In cases of suspected toxicity, TDM may be useful to dose-adjust.		Paradoxical interaction displaying short-term inhibition followed by induction at steady-state. • Short-term: ↑ voriconazole concentrations initially due to RTV-related CYP3A4 inhibition, particularly in CYP2C19 poor metabolizers. • Steady-state: ↓ voriconazole concentrations due to CYP2C19/2C9 induction. RTV 100 mg twice daily: 39% ↓ voriconazole AUC; 14% ↓ RTV AUC[45, 46] RTV 300 mg twice daily: 4.5- fold ↑ voriconazole AUC; 43% ↓ voriconazole clearance. More pronounced effect in CYP2C19 poor metabolizers 9- fold ↑ voriconazole AUC; 86% ↓ voriconazole clearance.[74] RTV 400 mg twice daily: 82% ↓ voriconazole AUC[45] Use of high-dose ritonavir (i.e. 400-600mg twice daily)

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
						with voriconazole is **contraindicated** due to significant reduction in voriconazole plasma concentrations.[46, 71] Use of low boosting doses of RTV (i.e. 100mg twice daily) combined with any of the other PIs should be **avoided** unless the benefits outweigh the risks of antifungal failure.[41, 46, 50, 61] Consider voriconazole TDM or use other antifungals that do not interact significantly with RTV.
Saquinavir (Primarily metabolized by CYP3A4 and P-gp. Weak inhibitor of CYP3A4 and P-gp.[57, 75])	Potential for ↑ concentrations of PIs and/or fluconazole via CYP 3A4 inhibition by both agents. Monitor for both PI and fluconazole toxicity (i.e. hepatotoxicity).	5-fold increase in saquinavir exposure when hard-gel capsules were coadministered with itraconazole 200 mg.[76] In a prospective randomized study in 17 HIV-infected subjects, saquinavir-sgc 800 or 1200 mg BID plus itraconazole 100 mg daily resulted in SQV concentrations equivalent to SQV-sgc 1400 mg BID alone.[77] Clinical significance unclear. Consider TDM of saquinavir.	Saquinavir 1200 mg TID plus ketoconazole 400 mg QD: 1.5-fold ↑ saquinavir AUC. Dosage adjustment not necessary.[75] Multiple dose study of SQV/r 1000/100mg BID and ketoconazole 200mg daily in healthy subjects resulted in ketoconazole ↑ AUC 168%, ↑ Cmax 45%. No substantial change in saquinavir and ritonavir exposures [78] Dosage adjustment not necessary with unboosted saquinavir. If using boosted saquinavir,	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.		

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
			ketoconazole doses > 200 mg/day not recommended.			
Tipranavir (Substrate of CYP3A4 and P-gp. Inducer of CYP3A4, P-gp, glucuronyl transferase, slight inducer of CYP2C9, moderate inducer of CYP1A2, and potent inhibitor of CYP2D6.[79] When co-administered with ritonavir, net effect is CYP3A inhibition.[80])	In healthy volunteers, coadministration of TPV 500/rtv 200 mg BID with fluconazole 100 mg QD resulted in 56%↑ AUC, 46% ↑ Cmax, 104% ↑ C12 of TPV; fluconazole PK parameters not significantly changed.[81] Fluconazole doses >200 mg/day are not recommended.[80]	Potential for ↑ concentrations of tipranavir and/or itraconazole via CYP 3A4 inhibition by both agents. Use combination with caution and monitor for dose-related toxicities (e.g., hepatotoxicity). Do not exceed itraconazole 200 mg daily.	Potential for increased ketoconazole and/or tipranavir concentrations. Use combination with caution and monitor for dose-related toxicities (e.g., hepatotoxicity). Do not exceed ketoconazole 200 mg daily.	Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.		Net effect difficult to predict given multiple CYP isoenzymes involved.[80] Potential ↑ or ↓ of one or both agents. Caution or avoid combination until further data are available.

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