

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. ketoconazole, itraconazole, clarithromycin). ⁹
Integrase Inhibitor						
Raltegravir (metabolized by UGT1A1 and has no inhibitory or inductive potential in vitro. ¹¹)	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.

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NNRTIs						
Delavirdine (metabolized via CYP3A4; also inhibits 3A4, as well as 2C9, 2C19. ¹²)	A dual inhibition interaction is possible via CYP 3A4 inhibition by delavirdine and fluconazole. No interaction noted. ¹³ 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. ¹³ Monitor for both delavirdine and ketoconazole toxicity (i.e. hepatotoxicity).	Possible ↑ delavirdine concentrations due to CYP3A4 inhibition by posaconazole. Monitor for delavirdine toxicity.		
Efavirenz (In vitro is a potent inducer and inhibitor of CYP3A4. Induces 2B6. ¹⁴ 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. ¹⁵ 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. ¹⁶ Case report of HIV-positive male with disseminated histoplasmosis with undetectable itraconazole concentrations and persistently elevated urinary <i>Histoplasma</i> antigen levels while on efavirenz and itraconazole 200 mg BID. Therapeutic itraconazole levels and a decrease in urinary <i>Histoplasma</i> antigen levels were observed after	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%. ¹⁹ Avoid concomitant use; consider alternate antiretroviral or antifungal therapy.	Posaconazole AUC ↓ 50% by efavirenz, ^{20, 21} 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.		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. ²² 55% ↓ voriconazole AUC; 1% ↑ efavirenz AUC when given as voriconazole 300 mg every 12 hours and efavirenz 300 mg daily. ²³ 7% ↓ voriconazole AUC; 17% ↑ efavirenz AUC when given as

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		<p>efavirenz was replaced with atazanavir/ritonavir.¹⁷</p> <p>In a retrospective cohort analysis, itraconazole levels were assessed in 10 HIV-positive patients with disseminated histoplasmosis; 4 patients were on PI 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.¹⁸</p> <p>No data using higher doses of itraconazole. 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.</p>				<p>voriconazole 400 mg every 12 hours and efavirenz 300 mg daily. These values are similar to monotherapy with either agent alone.²³</p> <p>Case report in 40 year-old male with mild HCV-related cirrhosis and cryptococcal 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.²⁴</p> <p>Contraindicated at standard doses.¹⁵</p> <p>Recommended dosage adjustment: ↑ voriconazole maintenance dose to 400 mg twice daily (from 200mg twice daily) ↓ 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.¹⁵</p> <p>Short-term co-administration (i.e. a</p>

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						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 inhibitor of CYP2C9 and a moderate inhibitor of CYP2C19. Also inhibits p-glycoprotein. No clinically relevant effect on CYP1A2 or CYP2D6. ^{25, 26})	In healthy volunteers, coadministration of etravirine 200 mg BID plus fluconazole 200 mg daily for 9 days resulted in 109% ↑ C _{min} , 75% ↑ C _{max} and 86% ↑ AUC of etravirine, while fluconazole parameters were unchanged compared to either drug administered alone. The combination was well tolerated. ²⁷ Use standard doses of both drugs. Monitor for side effects of etravirine.	Possible ↑ etravirine concentrations and/or ↓ concentrations of itraconazole. Dose adjustments for itraconazole may be necessary. ²⁵ Consider TDM of both drugs if possible.	Possible ↑ etravirine plasma concentrations and/or ↓ plasma concentrations of ketoconazole. ²⁵ Dose adjustments for ketoconazole may be necessary. Monitor for ketoconazole efficacy.	Possible ↑ etravirine concentrations due to CYP3A4 inhibition by posaconazole. ²⁵ No anticipated effect on posaconazole concentrations. Monitor for etravirine-related toxicity.		In healthy volunteers, coadministration of etravirine 200 mg BID plus voriconazole 200 mg BID for 9 days resulted in 52% ↑ C _{min} , 26% ↑ C _{max} and 36% ↑ AUC of etravirine, and 23% ↑ C _{min} 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. ²⁷ 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	In a healthy volunteer, cross-over study of itraconazole 200 mg QD, nevirapine 200 mg QD or the combination (each for 7 days), itraconazole C _{max} ↓ 38% and AUC ↓ 61% in the presence of nevirapine. Nevirapine	Ketoconazole levels sig. reduced (63% ↓ AUC, 40% ↓ C _{max} ,) 15-20% ↑ NVP concentrations. ³² 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.

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	<p>normal. Nevirapine did not affect the pharmacokinetics of fluconazole.²⁸ 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 patient on fluconazole developed clinical hepatitis.²⁹ 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.³⁰</p> <p>Use combination with caution. Monitor closely for nevirapine associated adverse effects including hepatotoxicity.</p>	<p>parameters were not changed.³¹ Dose adjustments for itraconazole may be necessary. Consider TDM of itraconazole if possible.</p>				
<p>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</p>	<p>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.³⁵</p>	<p>Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.³⁵</p>	<p>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%</p>	<p>Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.³⁵</p>		<p>Potential for increased concentrations of rilpivirine and decreased azole concentrations with concomitant administration. No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections.³⁵</p>

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effect on CYP3A activity is considered unlikely with phase III dose. ³³ No effect on CYP2E1 activity. ³⁴)	adjustment is required. Monitor for breakthrough fungal infections. ³⁵ .		compared to each agent alone. ³⁶ No rilpivirine dose adjustment is required. Monitor for breakthrough fungal infections. ³⁵			
PIs						
Atazanavir (Primarily metabolized by CYP3A4; also inhibits CYP3A and UGT1A1. ³⁷ Atazanavir alone does not induce glucuronidation, while atazanavir/ritonavir does induce glucuronidation. ³⁸)	In healthy subjects, coadministration of atazanavir 300/rtv 100 mg QD plus fluconazole 200 mg QD for 10 days did not result in changes to pharmacokinetic parameters of either ATV, rtv or fluconazole. ³⁹ Use standard doses of both drugs.	Potential for ↑ concentrations of PIs and/or itraconazole via CYP 3A4 inhibition by both agents. Clinical significance unclear, monitor for dose-related toxicities.	In a healthy volunteer study, coadministration of 400 mg atazanavir plus 200 mg ketoconazole daily did not result in significant changes in atazanavir concentrations. ⁴⁰ Dosage adjustment not necessary with unboosted atazanavir.	<u>Atazanavir</u> : 268% ↑ AUC atazanavir when given as 300 mg daily x 14 days with posaconazole 400 mg twice daily x 7 days <u>Atazanavir/RTV</u> : 146% ↑ AUC atazanavir when given as 300 mg/100 mg daily x 14 days with posaconazole 400 mg twice daily x 7 days. ^{20, 21} Empiric dosage adjustments are not recommended. Monitor for atazanavir-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. <ul style="list-style-type: none"> • <u>Short-term</u>: ↑ voriconazole concentrations initially due to RTV-related CYP3A4 inhibition, 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 ^{41, 42} 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. ^{37, 42}

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						<p>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.⁴³</p> <p>Consider voriconazole TDM or use other antifungals that do not interact significantly with RTV.</p>
<p>Darunavir (Primarily metabolized by CYP3A4. Inhibits CYP3A4.⁴⁴)</p>	<p>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).</p>	<p>Coadministration of darunavir 400/100 mg BID and ketoconazole 200 mg BID led to 212% ↑ ketoconazole exposure and 42% ↑ darunavir exposure.⁴⁵ A similar interaction may be possible with itraconazole. Do not exceed 200 mg itraconazole per day while on darunavir/ritonavir.</p>	<p>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.</p> <p>Coadministration of darunavir 400/100 mg BID and ketoconazole 200 mg BID in healthy volunteers (n=17) led to 212% ↑ ketoconazole exposure and 42% ↑ darunavir exposure.⁴⁵ Do not exceed 200 mg ketoconazole per day while on darunavir/ritonavir.</p>	<p>Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.</p>		<p>Paradoxical interaction displaying short-term inhibition followed by induction at steady-state.</p> <ul style="list-style-type: none"> • <u>Short-term:</u> ↑ voriconazole concentrations initially due to RTV-related CYP3A4 inhibition, particularly in CYP2C19 poor metabolizers. • <u>Steady-state:</u> ↓ voriconazole concentrations due to CYP2C19/2C9 induction. <p><u>With RTV 100 mg twice daily:</u> 39% ↓ voriconazole AUC; 14% ↓ RTV AUC^{41, 42}</p>

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						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. ^{42, 44} 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 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.

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						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. ⁴⁶
Fosamprenavir (Primarily metabolized by CYP3A4. Inhibitor of CYP3A4 (similar potency as indinavir and nelfinavir) ⁴⁷ ; also induces CYP3A4 ⁴⁸ .)	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. ⁴⁹ 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 ↓ 36% compared to fosamprenavir-ritonavir. Avoid posaconazole and unboosted fosamprenavir; optimal dosing of posaconazole and boosted fosamprenavir has not		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.

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				yet been determined. If concomitant therapy is required, use boosted fosamprenavir and consider TDM of both fosamprenavir and posaconazole. ⁵⁰		
Indinavir (Primarily metabolized by CYP3A4. Inhibitor of CYP3A4; may also be weak inhibitor of CYP2D6. ^{51, 52})	No clinically significant effect on indinavir AUC. ⁵² 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. ⁵² Consider reducing unboosted indinavir dose to 600 mg q8h.	Single-dose study of indinavir 400 mg and ketoconazole 400 mg: 68% ↑ indinavir AUC. ⁵² 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. ⁵³ 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 2C9. ⁵⁴)	Clinically significant interaction not expected. ⁵⁵ 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 significantly ↓. Lopinavir/r levels not affected. ⁵⁶ Similarly, in another case report of an HIV-positive patient with disseminated histoplasmosis infection, lopinavir concentrations	Single 200 mg ketoconazole dose had no significant effect on lopinavir/r concentrations. ⁵⁵ 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. <ul style="list-style-type: none"> • <u>Short-term:</u> ↑ voriconazole concentrations initially due to RTV-related CYP3A4 inhibition, particularly in CYP2C19 poor metabolizers. • <u>Steady-state:</u> ↓ voriconazole concentrations due to CYP2C19/2C9 induction.

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		remained stable after initiation of itraconazole 200 mg daily, and therapeutic antifungal levels (itraconazole + hydroxy-itraconazole) were achieved along with clinical response. ⁵⁷ Itraconazole doses >200 mg/day not recommended. ⁵⁵				With RTV 100 mg twice daily: 39% ↓ voriconazole AUC; 14% ↓ RTV AUC ^{41, 42} 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. ^{42, 55} Consider voriconazole TDM or use other antifungals that do not interact significantly with RTV.
Nelfinavir (Metabolized by CYP3A4 and CYP2C19. Inhibitor of CYP3A4. ^{58, 59} Induces CYP2B6, 2C8 and 2C9. ⁶⁰)	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. ⁶¹	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. ⁶² 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. ⁶³ 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. Consider TDM of both drugs.
Ritonavir (Potent inhibitor of CYP enzymes in following order: 3A>2D6>2C9, 2C19>>2A6, 2E1. Induces glucuronyl	12% ↑ RTV AUC. Clinical significance unclear. ⁶⁴ 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	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. ⁶⁴	80% ↑ AUC RTV with RTV 100mg daily x 14 days and posaconazole 400mg twice daily x 7 days. ²¹ RTV 600mg twice daily had no significant effect on		Paradoxical interaction displaying short-term inhibition followed by induction at steady-state. • <u>Short-term:</u> ↑ voriconazole concentrations

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transferases, CYP1A2, CYP2B6, CYP2C9 and CYP2C19. ⁵⁻⁷)		itraconazole were still detectable even 27 days after discontinuation of the drug. ⁶⁵ Use combination with caution and monitor for itraconazole-related toxicities (e.g., hepatotoxicity).	Ketoconazole doses >200 mg/day not recommended. Monitor for dose-related toxicities.	posaconazole concentrations. ⁶⁶ 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.		<p>initially due to RTV-related CYP3A4 inhibition, particularly in CYP2C19 poor metabolizers.</p> <ul style="list-style-type: none"> • <u>Steady-state:</u> ↓ voriconazole concentrations due to CYP2C19/2C9 induction. <p><u>RTV 100 mg twice daily:</u> 39% ↓ voriconazole AUC; 14% ↓ RTV AUC^{41, 42}</p> <p><u>RTV 300 mg twice daily:</u> 4.5- fold ↑ voriconazole AUC; 43% ↓ voriconazole clearance. More pronounced effect in CYP2C19 poor metabolizers 9- fold ↑ voriconazole AUC; 86% ↓ voriconazole clearance.⁶⁷</p> <p><u>RTV 400 mg twice daily:</u> 82% ↓ voriconazole AUC⁴¹</p> <p>Use of high-dose ritonavir (i.e. 400-600mg twice daily) with voriconazole is contraindicated due to significant reduction in voriconazole plasma concentrations.^{42, 64}</p> <p>Use of low boosting doses of RTV (i.e. 100mg twice daily)</p>

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						<p>combined with any of the other PIs should be avoided unless the benefits outweigh the risks of antifungal failure.^{37, 42, 44, 55}</p> <p>Consider voriconazole TDM or use other antifungals that do not interact significantly with RTV.</p>
<p>Saquinavir</p> <p>(Primarily metabolized by CYP3A4 and P-gp. Weak inhibitor of CYP3A4 and P-gp.^{51, 68})</p>	<p>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).</p>	<p>5-fold increase in saquinavir exposure when hard-gel capsules were coadministered with itraconazole 200 mg.⁶⁹ 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.⁷⁰ Clinical significance unclear. Consider TDM of saquinavir.</p>	<p>Saquinavir 1200 mg TID plus ketoconazole 400 mg QD: 1.5-fold ↑ saquinavir AUC. Dosage adjustment not necessary.⁶⁸</p> <p>Multiple dose study of SQV/r 1000/100mg BID and ketoconazole 200mg daily in healthy subjects resulted in ketoconazole ↑ AUC 168%, ↑ Cmax 45%.</p> <p>No substantial change in saquinavir and ritonavir exposures⁷¹ Dosage adjustment not necessary with unboosted saquinavir. If using boosted saquinavir, ketoconazole doses > 200 mg/day not recommended.</p>	<p>Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.</p>		
<p>Tipranavir</p> <p>(Substrate of CYP3A4 and P-gp. Inducer of CYP3A4, P-gp, glucuronyl transferase, slight</p>	<p>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</p>	<p>Potential for ↑ concentrations of tipranavir and/or itraconazole via CYP 3A4 inhibition by both agents. Use combination with</p>	<p>Potential for increased ketoconazole and/or tipranavir concentrations. Use combination with caution and monitor for dose-related</p>	<p>Possible ↑ PI concentrations due to CYP3A4 inhibition by posaconazole. Monitor for PI-related toxicity.</p>		<p>Net effect difficult to predict given multiple CYP isoenzymes involved.⁷³ Potential ↑ or ↓ of one or both agents. Caution or avoid combination</p>

	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Ravuconazole	Voriconazole
inducer of CYP2C9, moderate inducer of CYP1A2, and potent inhibitor of CYP2D6. ⁷² When co-administered with ritonavir, net effect is CYP3A inhibition. ⁷³)	TPV; fluconazole PK parameters not significantly changed. ⁷⁴ Fluconazole doses >200 mg/day are not recommended. ⁷³	caution and monitor for dose-related toxicities (e.g., hepatotoxicity). Do not exceed itraconazole 200 mg daily.	toxicities (e.g., hepatotoxicity). Do not exceed ketoconazole 200 mg daily.			until further data are available.

References:

1. Humphrey MJ, Jevons S, Tarbit MH. Pharmacokinetic evaluation of UK-49,858, a metabolically stable triazole antifungal drug, in animals and humans. *Antimicrob Agents Chemother* 1985;28:648-53.
2. Wang EJ, Lew K, Casciano CN, et al. Interaction of common azole antifungals with P glycoprotein. *Antimicrob Agents Chemother* 2002;46:160-5.
3. Black DJ, Kunze KL, Wienkers L, et al. Warfarin-fluconazole. II. A metabolically based drug interaction: in vivo studies. *Drug Metab Dispos* 1996;24:422-8.
4. Asgari M, Back DJ. Effect of azoles on the glucuronidation of zidovudine by human liver UDP-glucuronosyltransferase [letter; comment]. *Journal of Infectious Diseases* 1995;172(6):1634-6.
5. Sampol E, Lacarelle B, Rajaonarison JF, et al. Comparative effects of antifungal agents on zidovudine glucuronidation by human liver microsomes. *British Journal of Clinical Pharmacology* 1995;40(1):83-6.
6. Janssen-Ortho Inc. Sporanox (itraconazole) Product Monograph. Toronto 2008.
7. Takano M, Hasegawa R, Fukuda T, et al. Interaction with P-glycoprotein and transport of erythromycin, midazolam and ketoconazole in Caco-2 cells. *European Journal of Pharmacology* 1998;358(3):289-94.
8. Bruggemann RJM, Alffenaar J-WC, Blijlevens NMA, et al. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other co-administered agents. *Clin Infec Dis* 2009;48:1441-58.
9. Pfizer Canada Inc. Celsentri (maraviroc) Product Monograph. Kirkland, QC 2009.
10. Abel S, Russell D, Ridgway C, et al. Overview of the drug-drug interaction data for maraviroc (UK-427,857) [abstract 76]. 6th International Workshop on Clinical Pharmacology of HIV Therapy April 28-30, 2005, Quebec.
11. Merck Frosst Canada Ltd. Isentress (raltegravir) Prescribing Information. Kirkland, QC 2009.
12. Tran JQ, Petersen C, Garrett M, et al. Delavirdine significantly increases plasma concentrations of amprenavir in healthy volunteers. *AIDS* 2000;14 (supplement 4):S92.
13. Pfizer Canada Inc. Rescriptor (delavirdine) Product Monograph. Kirkland, QC 2004.

14. Robertson SM, Maldarelli F, Natarajan V, et al. Efavirenz induces CYP2B6-mediated hydroxylation of bupropion in healthy subjects. *J Acquir Immune Defic Syndr* 2008;49(5):513-9.
15. Bristol-Myers Squibb Canada. Sustiva (efavirenz) Prescribing Information. Montreal, QC 2008.
16. Kaul S, Ji P, Dudley J, et al. Pharmacokinetic interaction between efavirenz and diltiazem or itraconazole after multiple-dose administration in adult healthy subjects [abstract 561]. 14th Conference on Retroviruses and Opportunistic Infections February 25-28th 2007, Los Angeles CA.
17. Koo HL, Hamill RJ, Andrade RA. Drug-drug interaction between itraconazole and efavirenz in a patient with AIDS and disseminated histoplasmosis *Clinical Infectious Diseases* 2007;45:e77-79.
18. Andrade RA, Evans RT, Hamill RJ, et al. Clinical evidence of interaction between itraconazole and nonnucleoside reverse transcriptase inhibitors in HIV-infected patients with disseminated Histoplasmosis. *Ann Pharmacother* 2009;43:908-13.
19. Sriwiriyan S, Mahatthanatrakul W, Ridditid W, et al. Effect of efavirenz on the pharmacokinetics of ketoconazole in HIV-infected patients. *Eur J Clin Pharmacol* 2007;63(5):479-83.
20. Krishna G, Moton a, Ma L, et al. Effects of oral posaconazole on the pharmacokinetics of atazanavir alone and with ritonavir or with efavirenz in healthy adult volunteers. *J Acquir Immune Defic Syndr* 2009;51:437-44.
21. Schering-Plough. Noxafil (posaconazole) Product Monograph. Kenilworth, NJ 2009.
22. Liu P, Foster G, LaBadie RR, et al. Pharmacokinetic interaction between voriconazole and efavirenz at steady state in healthy male subjects. *J Clin Pharmacol* 2008;48(1):73-84.
23. Damle B, LaBadie R, Crownover P, et al. Pharmacokinetic interactions of efavirenz and voriconazole in healthy volunteers. *Br J Clin Pharmacol* 2008;65(4):523-30.
24. Carbonara S, Regazzi M, Ciraci E, et al. Long-term efficacy and safety of TDM-assisted combination of voriconazole plus efavirenz in an AIDS patient with cryptococcosis and liver cirrhosis. *Ann Pharmacother* 2009;43:978-84.
25. Tibotec I. Intelence (etravirine) Product Monograph. Raritan, NJ, USA 2009.
26. Scholler-Gyure M, Kakuda TN, Stevens T, et al. Effect of etravirine on cytochrome P450 isozymes assessed by the Cooperstown 5+1 cocktail [abstract A-955]. . 48th Interscience Conference on Antimicrobial Agents and Chemotherapy, October 25-28, 2008, Washington, DC.
27. Scholler-Gyure M, Kakuda TN, Van Solingen-Ristea R, et al. Pharmacokinetic interaction between etravirine and fluconazole or voriconazole in HIV-negative volunteers [abstract A1-1299]. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 12-15, 2009, San Francisco.
28. Geel J, Pitt J, Orrell C, et al. The effect of fluconazole on nevirapine pharmacokinetics [abstract WeOrB1239]. XV International AIDS Conference, July 11-16, 2004, Bangkok, Thailand.
29. Manosuthi W, Athichathanabadi C, Uttayamakul S, et al. Plasma nevirapine levels, adverse events and efficacy of antiretroviral therapy among HIV-infected patients concurrently receiving nevirapine-based antiretroviral therapy and fluconazole. *BMC Infect Dis* 2007;7:14-21.
30. Wakeham K, Parkes-Ratanshi R, Watson V, et al. Co-administration of fluconazole increases nevirapine concentrations in HIV-infected Ugandans. *J Antimicrob Chemother* 2010;65(2):316-9.

31. Jaruratanasirikul S, Sriwiryajan S. Pharmacokinetic study of the interaction between itraconazole and nevirapine. *Eur J Clin Pharmacol* 2007;63(5):451-6.
32. Lamson M, Robinson P, Gigliotti M, et al. The pharmacokinetic interactions of nevirapine and ketoconazole [abstract 12218]. 12th World AIDS Conference, June 28-July 3, 1998, Geneva, Switzerland.
33. Crauwels HM, Van Heeswijk R, Stevens T, et al. The effect of TMC278, a next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) on CYP3A activity in vivo [abstract P_28]. 10th International Workshop on Clinical Pharmacology of HIV Therapy, April 15-17, 2009, Amsterdam.
34. Van Heeswijk RP, al. E. The effects of TMC 278, a next generation non-nucleoside reverse transcriptase inhibitor, on the pharmacokinetics of acetaminophen and CYP2E1 activity in HIV-negative volunteers [abstract 67]. 8th International Workshop on Clinical Pharmacology of HIV Therapy, April 16-18, 2007, Budapest, Hungary.
35. Tibotec Inc. Edurant (rilpivirine) Product Monograph. Raritan, NJ 2011.
36. Van Heeswijk RP, hoetelmans RM, Kestens D, et al. The pharmacokinetic interaction between ketoconazole and TMC278, an investigational non-nucleoside reverse transcriptase inhibitor in healthy, HIV-negative subjects [abstract TUPE0087]. XVI International AIDS Conference, August 13-18 2006, Toronto, Canada.
37. Bristol-Myers Squibb Canada. Reyataz (atazanavir) Product Monograph. Montreal, QC 2008.
38. Burger D, Huisman A, Van Ewijk N, et al. The effect of atazanavir and atazanavir/ritonavir on UGT1A4 using lamotrigine as a phenotypic probe [abstract 566]. 14th Conference on Retroviruses and Opportunistic Infections, February 25-28th 2007, Los Angeles CA.
39. Agarwala S, Gray K, Nettles R, et al. Lack of pharmacokinetic interaction between atazanavir, ritonavir and fluconazole dosed to steady-state in healthy subjects [abstract A-0382]. 46th Interscience Conference on Antimicrobial Agents and Chemotherapy September 27-30 2006, San Francisco, CA.
40. O'Mara E, Randall D, Uderman H, et al. Steady-state pharmacokinetic interaction study between BMS-232632 and ketoconazole in healthy subjects [abstract 1646]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17-20, 2000, Toronto, Canada.
41. Liu P, Foster G, Gandelman K, et al. Steady state pharmacokinetic and safety profiles of voriconazole and ritonavir in healthy male subjects. *Antimicrobial Agents and Chemotherapy* 2007;51(10):3617-26.
42. Pfizer Canada Inc. Vfend (voriconazole) Product Monograph. Kirkland, Quebec 2009.
43. Gibson JN, Fulco PP. Concurrent atazanavir and voriconazole in a patient with multidrug-resistant HIV and a mycetoma *AIDS* 2011;25(16):2054-6.
44. Janssen-Ortho Inc. Prezista (darunavir) Product Monograph. Toronto, Ontario 2009.
45. Sekar V, Lefebvre E, De Pauw M, et al. Pharmacokinetics of darunavir/ritonavir and ketoconazole following co-administration in HIV-healthy volunteers. *British Journal of Clinical Pharmacology* 2008;66(2):215-21.
46. Toy J, Giguère P, Kravcik S, et al. Drug interactions between voriconazole, darunavir/ritonavir and etravirine in an HIV-infected patient with Aspergillus pneumonia. *AIDS* 2011;25(4):541-2.
47. GlaxoSmithKline. Telzir (fosamprenavir) Prescribing Information. Mississauga, ON 2009.
48. GlaxoSmithKline. Lexiva (fosamprenavir) Product Monograph. Research Triangle Park, NC 2007.

49. Polk RE, Crouch M, Israel DS, et al. Pharmacokinetic interaction between ketoconazole and amprenavir after single doses in healthy men. *Pharmacotherapy* 1999;19(12):1378-84.
50. Brüggemann RJM, van Luin M, Colbers EPH, et al. Effect of posaconazole on the pharmacokinetics of fosamprenavir and vice versa in healthy volunteers. *J Antimicrob Chemother* 2010;65(10):2188-94.
51. Eagling VA, Back DJ, Barry MG. Differential inhibition of cytochrome P450 isoforms by the protease inhibitors, ritonavir, saquinavir and indinavir. *British Journal of Clinical Pharmacology* 1997;44(2):190-4.
52. Merck Frosst Canada Ltd. Crixivan (indinavir) Prescribing Information. Kirkland, QC 2009.
53. Purkins L, Wood N, Kleinermans D, et al. No clinically significant pharmacokinetic interactions between voriconazole and indinavir in healthy volunteers. *British Journal of Clinical Pharmacology* 2003;56(Suppl 1):62-8.
54. Yeh R, Gaver V, Patterson K, et al. Lopinavir/ritonavir induces the hepatic activity of cytochrome P450 enzymes CYP2C9, CYP2C19, and CYP1A2 but inhibits the hepatic and intestinal activity of CYP3A as measured by a phenotyping drug cocktail in healthy volunteers. *J Acquir Immune Defic Syndr* 2006;42:52-60.
55. Abbott Laboratories Limited Canada. Kaletra (lopinavir/ritonavir) Prescribing Information. Saint Laurent, Canada 2009.
56. Crommentuyn KM, Mulder JW, Sparidans RW, et al. Drug-drug interaction between itraconazole and the antiretroviral drug lopinavir/ritonavir in an HIV-1-infected patient with disseminated histoplasmosis. *Clinical Infectious Diseases* 2004;38(8):e73-75.
57. Hills-Nieminen C, Hughes C, Houston S, et al. Drug-drug interaction between itraconazole and the protease inhibitor lopinavir/ritonavir. *Ann Pharmacother* 2009;43:2117-20.
58. Lee CA, Liang BH, Wu EY, et al. Prediction of nelfinavir mesylate (VIRACEPT) clinical drug interactions based on in vitro human P450 metabolism studies. 4th National Conference on Retroviruses and Opportunistic Infections, January 22-26, 1997, Washington DC.
59. Pfizer Canada Inc. Viracept (nelfinavir) Prescribing Information. Kirkland, QC 2008.
60. Dixit V, Hariparsad N, Li F, et al. Cytochrome P450 enzymes and transporters induced by anti-human immunodeficiency virus protease inhibitors in human hepatocytes: implications for predicting clinical drug interactions. *Drug Metab Dispos* 2007;35(10):1853-9.
61. Kerr B, Yuen G, Daniels R, et al. Strategic approach to nelfinavir mesylate (NFV) drug interactions involving CYP3A metabolism. 4th National Conference on Retroviruses and Opportunistic Infections, 1997, Washington DC.
62. Kerr B, Lee C, Yuen G, et al. Overview of in-vitro and in-vivo drug interaction studies of nelfinavir mesylate, a new HIV-1 protease inhibitor [abstract 373]. 4th Conference on Retroviruses and Opportunistic Infections, January 22-26, 1997, Washington DC.
63. Yan J, Marino MR, Smith RA, et al. The effect of ravuconazole on the pharmacokinetics of nelfinavir in healthy male volunteers. *J Clin Pharmacol* 2006;46:193-200.
64. Abbott Laboratories Limited Canada. Norvir (ritonavir) Prescribing Information. Saint-Laurent, QC 2008.
65. MacKenzie-Wood AR, Whitfeld MJ, Ray JE. Itraconazole and HIV protease inhibitors: an important interaction (letter). *Medical Journal of Australia* 1999;170:46-47.

66. Schering-Plough Canada Inc. Posanol (posaconazole) Product Monograph. Kirkland, Quebec 2008.
67. Mikus G, Schowel V, Drzewinska M, et al. Potent cytochrome P450 2C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. *Clin Pharmacol Ther* 2006;80:126-35.
68. Hoffmann-La Roche Ltd. Invirase (saquinavir) Prescribing Information. Mississauga, ON 2008.
69. Koks CH, van Heeswijk RP, Veldkamp AI, et al. Itraconazole as an alternative for ritonavir liquid formulation when combined with saquinavir. *AIDS* 2000;14(1):89-90.
70. Cardiello P, Samor T, Burger D, et al. Pharmacokinetics of lower doses of saquinavir soft gel caps (800- and 1200-mg BID) with itraconazole compared to 1400 mg SQV BID without itra in HIV-1+ Thai patients [abstract 447-W]. 9th Conference on Retroviruses and Opportunistic Infections, February 24-28, 2002, Seattle, WA.
71. Kaeser B, Zandt H, Bour F, et al. Drug-drug interaction study of ketoconazole and ritonavir-boosted saquinavir. *Antimicrob Agents Chemother* 2009;53(2):609-14.
72. Vourvahis M, Dumond J, Patterson K, et al. Effects of tipranavir/ritonavir on the activity of cytochrome p450 enzymes 1A2, 2C9 and 2D6 in healthy volunteers [abstract 52]. 8th International Workshop on Clinical Pharmacology of HIV Therapy, April 16-18, 2007, Budapest, Hungary.
73. Boehringer Ingelheim. Aptivus (tipranavir) Prescribing Information. . Burlington, ON 2009.
74. La Porte CJL, Sabo JP, Elgadi M, et al. Interaction studies of tipranavir-ritonavir with clarithromycin, fluconazole, and rifabutin in healthy volunteers. *Antimicrob Agents Chemother* 2009;53(1):162-73.