

Drug Interactions of Tipranavir, a New HIV Protease Inhibitor

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Abstract: Tipranavir is one of the latest approved HIV protease inhibitors. This non-peptidic molecule is a strong inducer of cytochrome P450 and has to be co-administered with low doses ritonavir as pharmacokinetic booster to achieve effective antiviral activity in vivo. As expected, significant drug interactions may occur in patients treated with tipranavir/ritonavir, including diminished exposure to some antiretroviral agents. Although a few interactions can be managed with adequate drug dosing others preclude to use these medications in combination.

Key Words: Tipranavir, HIV, drug interactions, protease inhibitors.

Tipranavir (TPV) has recently been approved for the treatment of antiretroviral-experienced HIV-infected patients (Aptivus®, Boehringer-Ingelheim). As nelfinavir and in contrast with the rest of HIV protease inhibitors (PI), TPV is a non-peptidic HIV molecule, which has to be administered with ritonavir (r) as a booster to achieve optimal antiviral concentrations. The recommended doses are TPV/r 500/200 mg twice daily [1-3]. The TPV interaction profile is rather complex due to the conflicting effects of TPV/r on CYP3A4 and P-glycoprotein (P-gp). While TPV induces CYP3A4 and P-gp, ritonavir is a strong inhibitor of these enzymatic complexes and membrane transporters, respectively. Moreover, it is well established that TPV inhibits CYP1A2, 2C9, 2C19 and 2D6, but the effects of ritonavir on these enzymes is so far unclear.

Nucleoside reverse transcriptase inhibitors (NRTI) are widely used as part of antiretroviral regimens. They are not metabolised by CYP3A4 nor substrates of P-gp. Therefore, TPV should not affect NRTI exposure. However, reductions in NRTI exposure have been observed when these agents are co-administered with TPV/r. The clinical significance of these findings is unknown and no dosage restrictions have been recommended but for didanosine (ddI). As TPV is advised to be administered with food and ddI has to be administered on an empty stomach, ddI should be taken preferably 1 hour or 2 hours after TPV/r [4].

There is no significant interaction between TPV/r and commercially available nonnucleoside reverse transcriptase inhibitors (NNRTI), namely efavirenz or nevirapine. However, the combination of TPV/r with etravirine (TMC125), a new generation NNRTI, has shown a 76% reduction in etravirine area under the curve (AUC), while conversely TPV and RTV exposure are increased by 18% and 23%, respectively. These findings suggest that etravirine and TPV/r should not be used together [4-6].

In general, the concentration of other PI is reduced when they are co-administered with TPV/r, due to an inducing effect on P-gp and possibly other transporter molecules.

Although the clinical significance of these interactions has not been fully elucidated, coadministration of PI with TPV/r is not recommended [7]. If a dual boosted PI combination wants to be used, therapeutic drug monitoring may be warranted to guide adequate dose adjustments.

An unexpected interaction between TPV/r and enfuvirtide (ENF), an HIV entry inhibitor, has recently been described in a study of 39 patients [8]. Although plasma trough concentrations of both TPV and RTV were significantly increased in the 20 patients receiving ENF, the clinical significance of this interaction is unknown and there are not currently guidelines to modify doses or against the use of these antiretrovirals in combination. Moreover, the results from clinical trials suggest that the use of TPV/r along with ENF provides high rates of virological suppression even among heavily antiretroviral-experienced patients [1-3,9]. Table 1 summarises the main information available on interactions between TPV/r and other antiretroviral drugs [4-6].

With respect to other antimicrobial agents, a pharmacokinetic study has recently shown an increase in TPV and clarithromycin exposure when they are co-administered. However, dose adjustments of TPV or clarithromycin are not recommended for patients with normal renal function. Coadministration of TPV/r and rifampicin may cause large reductions in TPV concentrations due to the potent induction of CYP3A4 by rifampicin. Thus, the concomitant use of TPV and rifampicin is contraindicated. Alternative antituberculous agents such as rifabutin should be considered in this situation but using lower doses of rifabutin than usually recommended, for example of 150 mg three times a week [10].

The antifungal agent fluconazole increases significantly TPV exposure, either C_{max}, AUC and C_{min}. Although dose adjustments are not recommended, fluconazole doses greater than 200 mg/day should not be prescribed. On the other hand, TPV/r may increase itraconazole or ketoconazole concentrations, and therefore these agents should be used with caution in patients taking TPV/r and doses above 200 mg/day have to be discouraged. In contrast, voriconazole, a new antifungal agent, is reduced when coadministered with TPV/r [4]. For this reason and until further data will be available, their coadministration should be discouraged. Table 2 summarises the main information available about interactions between TPV/r and other medications [4-6].

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Table 1. Summary of Tipranavir/Ritonavir Interactions with other Antiretroviral Drugs

Family	Drug	Interaction	Recommendation
NRTI	AZT	↓ 35% AUC AZT	No dose adjustment recommended; clinical significance unknown.
	3TC	↓ 27% AUC 3TC	
	d4T	↓ 15 % AUC d4T	
	ABC	↓ 40 % AUC ABC	
	ddI	↓ 46% AUC ddI	For optimal absorption, ddI should be separated from TPV/r dosing by at least 2 hours.
NNRTI	NVP	No significant interactions documented	Contraindicated
	EFV		
	etravirine (TMC125)	↓ 76% AUC TMC125 ↑ 18% AUC TPV	
PI	LPV	↓ 49% AUC LPV	Combination not recommended.
	SQV	↓ 70% AUC SQV	
	APV	↓ 56% AUC APV	
	ATV	↓ 81 % Cmin ATV	
Fusion Inhibitors	enfuvirtide	↑ 53% Cmin TPV	Clinical significance unknown.

AUC: area under the curve; Cmin: minimal concentration in steady-state; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor; AZT: zidovudine; 3TC: lamivudine; d4T: stavudine; ABC: abacavir; ddI: didanosine; NVP: nevirapine; EFV: efavirenz; LPV: lopinavir; RTV: ritonavir; SQV: saquinavir; AMP: amprenavir; ATV: atazanavir, HMG-CoA: hydroxymethylglutaryl - coenzyme A; PDE5: phosphodiesterase 5.

Table 2. Summary of Tipranavir/Ritonavir Interactions with other Medications

Family	Drug	Interaction	Recommendation
Antiinfectious agents	Clarithromycin	↑ 66% AUC TPV ↑ 19% AUC Clarithromycin ↓ 97% AUC 14-OH-clarithromycin	Patients with renal impairment: reduce dose of clarithromycin by 50% for CrCl 30-60mL/min and by 75% for CrCl < 30mL/min.
	Rifampicin	Significant ↓ TPV levels.	Contraindicated
	Rifabutin	↑ Rifabutin concentrations by up to 3-fold and its metabolite by up to 20-fold.	Reduce dose to 150 mg three times a week.
	Fluconazole	↑ 50% AUC TPV	Antifungal doses > 200 mg/day are not recommended.
	Itraconazole Ketoconazole	Potential ↑ AUC itraconazole and ketoconazole.	
	Voriconazole	Potential ↓ AUC voriconazole and TPV/r	Combination not recommended
Gastric acid suppressive therapies	Antiacids (Mg, Al)	↓ 25-29% AUC, Cmax and Cmin TPV	For optimal absorption, separate dose timing.
	Proton pump inhibitors, H2-receptor antagonists	Expected ↓ AUC TPV	
HMG-CoA reductase inhibitors	Simvastatin, Lovastatin	Severe ↑ statin levels.	Contraindicated
	Atorvastatin	↑ 8.6 fold AUC atorvastatin	Combination not recommended. Start with the low possible dose of atorvastatin with careful monitoring or consider other HMG-CoA reductase inhibitor.
Oral hypoglycemic agents	Glipizide, Tolbutamide	Effect unknown.	Glucose monitoring is recommended.

(Table 2. Contd....)

Family	Drug	Interaction	Recommendation
Antiarrhythmics	Amiodarone, Bepridil, Quinidine	Significant ↑ plasma concentrations expected associated with serious and/or life threatening events.	Contraindicated
Antihistamines	Astemizole, Terfenadine		
Ergot derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergotamine,		
GI motility agents	Cisapride		
Anxiolytics and hypnotics	Midazolam Triazolam		
Neuroleptics	Pimozide		
Narcotic analgesics	Methadone	↓ 53% AUC methadone.	Dosage of methadone may need to be increased.
Antimotility agents	Loperamide	↓ 63% AUC loperamide ↓ 26% Cmin TPV	The clinical relevance is unknown.
Antidepressants	SSRIs, TCAs, Trazodone	Potential ↑ antidepressants plasma concentrations.	Dosage reduction and concentration plasma monitoring is recommended.
Herbal products	St. John's wort	Potential ↓ TPV concentrations.	Contraindicated
	Garlic	Potential ↓ TPV concentrations	Combination not recommended
Calcium channel blockers	Diltiazem, Felodipine, Nicardipine, Nisoldipine, Verapamil	Effect unknown.	Caution and clinical monitoring of patient is warranted.
Immunosuppressors	Cyclosporine, Tacrolimus, Sirolimus	Effect unknown.	Monitoring immunosuppressor levels is recommended.
Corticosteroids	Budesonide, Fluticasone	Potential ↑ corticosteroids levels.	Combinations not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.
PDE inhibitors	Sildenafil, Tadalafil, Vardenafil	Potential ↑ PDE inhibitor levels.	Do not exceed 25 mg of sildenafil in 48 h, 10 mg of tadalafil in 72 h or 2.5 mg of vardenafil in 72 h.
Estrogens	Ethinyl estradiol	↓ 50% AUC ethinyl estradiol	If used as contraceptive, alternative methods of non-hormonal contraception should be considered. If used as hormone replacement therapy, monitor for signs of estrogen deficiency.

TPV, tipranavir; PDE, phosphodiesterase inhibitors; SSRIs, selective serotonin reuptake inhibitors; AUC, area under the curve; Cmax, maximal concentration; Cmin, minimal concentration.

Few data are available about the pharmacokinetic effects of gastric acid suppressive agents on TPV exposure. One study evaluated the concurrent administration of TPV/r 500/200 mg (single dose) with 20 mL of an aluminium/magnesium-based antacid. A statistically significant decrease in the AUC, Cmax and Cmin of TPV by 25-29% was reported. Therefore, antacids should be administered separately from TPV/r. With regard to proton pump inhibitors or H₂-receptor antagonists, no data are so far available about their impact on TPV exposure. However, reduced plasma concentrations of TPV may occur due to increased gastric pH if these drugs are administered together.

Lipid lowering agents are extensively metabolised by the CYP3A4 system. Co-administration of TPV/r with simvastatin or lovastatin is contraindicated due to significant in-

creases in simvastatin and lovastatin levels, which may produce adverse effects such as myopathy and/or rhabdomyolysis. Likewise, coadministration of atorvastatin and TPV/r results in increased exposure of atorvastatin, and therefore this combination should not be recommended. Alternatively, atorvastatin may be started using the lowest doses and followed by steadily increases with careful monitoring. When possible, in patients taking TPV/r other HMG-CoA reductase inhibitors should be considered such as pravastatin, fluvastatin or rosuvastatin [4-6].

The anticoagulant warfarin and the hypoglycaemic agents glipizide and tolbutamide are substrates of CYP2C9. At this time, the effect of TPV/r on CYP2C9 is unknown. Therefore, close monitoring of INR (International Normalized Ratio) and glucose is recommended in HIV patients

who have to be treated with TPV/r and are receiving these compounds.

The combination of TPV/r with cardiovascular agents such as calcium channel blockers (i.e., diltiazem, felodipine, nifedipine, nisoldipine, verapamil) is complicated by the fact that they are substrates of CYP3A and P-gp. The final consequences of their coadministration can not be predicted due to conflicting effects of TPV/r on CYP3A and P-gp. Thus, caution and clinical monitoring of these patients is warranted.

Coadministration of TPV/r with medications that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events is contraindicated. Among these drugs the following should preferentially keep in mind: antiarrhythmics such as amiodarone, bepridil and quinidine; neuroleptics such as pimozide; anxiolytics such as midazolam and triazolam; antihistaminics such as astemizole and terfenadine; ergotic derivatives such as dihydroergotamine, ergonovine, ergotamine and methylergonovine; and the antiemetic agent cisapride [4-6].

TPV/r significantly reduces total methadone exposure possibly by inducing intestinal P-gp. Thus, increased doses of methadone may be required to avoid opioid withdrawal symptoms [4]. This consideration is important given that a substantial proportion of HIV-infected patients have been drug users and currently may be under methadone substitution programmes.

Drug interactions between TPV/r and some antidepressants such as desipramine, sertraline, paroxetine and fluoxetine have not been well characterised. However, exposure to these agents should be expected to be increased when coadministered with TPV/r. Therefore, dosage reductions, therapeutic drug monitoring and careful monitoring are warranted. The concomitant use of trazodone, an anxiety relief agent, with TPV/r may result in increased trazodone plasma concentrations. Adverse events such as nausea, dizziness, hypotension and syncope have occasionally been reported in patients taking trazodone and RTV. Therefore, trazodone should be avoided or used with caution, beginning always with low doses in patients receiving TPV/r [4-6].

Special mention merits some supplemental herbal products, such as garlic, which induces CYP3A4 and P-gp. Coadministration with TPV/r should be discouraged. Given that St John's wort (*Hypericum perforatum*) is a potent CYP3A4 inducer [11], it may reduce the bioavailability of TPV/r. Therefore it should be avoided in patients who have to be treated with TPV/r in order to minimize the risk of virological failure and selection of drug resistance.

The effect of TPV/r on immunosuppressive agents, such as cyclosporine, tacrolimus and sirolimus is somewhat unpredictable, due to conflicting effects of TPV/r on CYP3A and P-gp. Therefore frequent monitoring of these drugs is recommended until blood levels have been stabilized in a given patient. A dose reduction of glucocorticoids (budesonide, fluticasone) should be considered with close monitoring of local and systemic effects or switch to alternative glucocorticoids (e.g., beclomethasone) which are not CYP3A4 substrates. The concomitant use of phosphodiesterase inhibitors and TPV/r may result in increased exposure to sildenafil, tadalafil and vardenafil. Therefore, reduced dosages of these agents have been recommended. Given that TPV/r decrease ethinyl estradiol AUC in 50%, the efficacy of these anticonceptive agents may be compromised in women taking these drugs concomitantly. Finally, given that TPV soft capsules contain alcohol (7% ethanol) [4-6], disulfiram-like reactions may be seen when treated patients are exposed to disulfiram or other drugs that prone to this reaction (e.g. metronidazole).

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REFERENCES

- [1] Gathe, J.; Cooper, D.; Farthing, C.; Jayaweera, D.; Norris, D.; Pierone, G.; Steinhart, C.R.; Trottier, B.; Walmsley, S.; Workman, C.; Mukwava, G.; Kohlbrenner, V.; Dohnanvi, C.; McCallister, S.; Mayers, D.; RESIST-1 Study Group. *Clin. Infect. Dis.* **2006**, *43*, 1337-46.
- [2] Cahn, P.; Villacian, J.; Lazzarin, A.; Katlama, C.; Grinsztejn, B.; Araste, K.; Lopez, P.; Clumeck, N.; Gerstoft, J.; Stavrienas, N.; Antunes, F.; Neubacher, D.; Mayers, D. *Clin. Infect. Dis.* **2006**, *43*, 1347-56.
- [3] Hicks, C.; Cahn, P.; Cooper, D.; Walmsley, S.; Katlama, C.; Clotet, B.; Lazzarin, A.; Johnson, M.; Neubacher, D.; Mayers, D.; Valdez, H.; RESIST Investigator Group. *Lancet* **2006**, *368*, 466-75.
- [4] Boffito, M.; Maitland, D.; Pozniak, A. *J. Clin. Pharmacol.* **2006**, *46*, 130-9.
- [5] King, J.; Acosta, E. *Clin. Pharmacokinet.* **2006**, *45*, 665-82.
- [6] Dong, B.; Cocohoba, J. *Ann. Pharmacother.* **2006**, *40*, 1311-21.
- [7] Hammer, S.; Saag, M.; Schecheter, M.; Montaner, J.; Schooley, R.; Jacobsen, D.; Thompson, M.; Carpenter, C.; Gazzard, B.; Gatell, J.; Hirsch, M.; Katzenstein, D.; Richman, D.; Vella, S.; Yeni, P.; Volberding, P. International AIDS Society-USA Panel. *JAMA* **2006**, *296*, 827-43.
- [8] De Requena D.G., Calcagno, A.; Bonora, S.; Ladetto, L.; D'Avolio, A.; Sciandra, M.; Siccardi, M.; Bargiacchi, O.; Sinicco, A.; Di Perri, G. *AIDS* **2006**, *20*, 1977-9.
- [9] De Mendoza, C.; Valer, L.; Ribera, E.; Barreiro, P.; Martín-Carbonero, L.; Ramirez, G.; Soriano, V. *HIV Clin. Trials* **2006**, *7*, 163-71.
- [10] Moreno, S.; Hernandez, B.; Dronza, F. *AIDS Rev.* **2006**, *8*, 115-24.
- [11] Patel, J.; Buddha, B.; Dey, S.; Pal, D.; Mitra, A. *Am. J. Ther.* **2004**, *11*, 262-77.