Perspective

Drug-Drug Interactions that Matter

It is increasingly difficult to keep track of information on drug-drug interactions in HIV therapeutics, and the clinical implications of much of the data reported are not immediately evident. Nevertheless, knowledge of drug-drug interactions is necessary to preserve antiretroviral efficacy and to avoid undue risk of toxicity. The following article reviews important drug-drug interactions and accumulating data on newer antiretroviral agents. The article summarizes a presentation made by David J. Back, PhD, at the International AIDS Society–USA course in New York in March 2006

Data on drug-drug interactions in HIV therapeutics continue to accumulate at a rapid pace. The clinical significance of such information, however, is not always clear. Some of the reported information is contradictory or counterintuitive. Further, it is not always easy to determine whether interactions affect the balance between antiretroviral activity and the risk for drug-related adverse effects. The matter is also complicated by the wide interindividual variability in drug pharmacokinetics; differences between individual patients can depend on such factors as genetic differences, sex, inherent variability in drug formulations, drug-food interactions, and drug-disease interactions. Despite the complexities, potential drug interactions must be considered when starting or changing anti-retroviral therapy. In general, medications with the lowest potential for interactions should be selected for use. Good resources on HIV pharmacology include the following Web sites: www.hivdruginteractions.org; www.tthhivclinic.com; http://hivinsite.ucsf.edu; www.hivpharmacology.com; and http://clinicaloptions.com.

Some Key Antiretroviral Drug Interactions

Some key interactions of protease inhibitors (PIs) with other PIs or nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) are shown in Table 1. As shown, the combination of tipranavir and lopinavir is not recommended due to a marked decrease in lopinavir exposure. However, a recent small study examined whether increasing lopinavir doses might overcome this effect (Harris et al, CROI, 2006). In this study, 13 HIV-infected patients receiving ritonavir-boosted (r) lopinavir 400 mg/100 mg twice daily and no other PIs or NNRTIs were given tipranavir 500 mg twice daily and either (1) lopinavir/r 400 mg/300 mg twice daily or (2) lopinavir/r 533 mg/233 mg twice daily. At 14 days, neither group had lopinavir trough concentrations different from those prior to the addition of tipranavir and dose changes; however, there was marked interpatient variability in these concentrations (Figure 1). Such findings suggest that the combination should be considered only if TDM is used to guide dosing in individual patients.

In fact, tipranavir/r is likely to have a somewhat complicated interaction profile because it affects levels of other drugs via more than 1 mechanism. With coadministered PIs, the effect of tipranavir/r is likely mediated to a large extent by an inducing effect on P-glycoprotein and possibly other transporter molecules. With other drugs, the net *in vivo* effect of tipranavir/r is inhibition of cytochrome P450 (CYP) 3A4, as a result of ritonavir inhibiting this enzyme (ie, the inhibition by ritonavir is greater than

Table **1**. Selected Key Protease Inhibitor-Protease Inhibitor and Protease Inhibitor-Nonnucleoside Analogue Reverse Transcriptase Inhibitor Interactions

Regimen	Drug Concentration		Comment
Lopinavir/r + Saquinavir	Lopinavir ↔	Saquinavir ↔	N
Lopinavir/r + Fosamprenavir	Lopinavir ↓	Fosamprenavir ↓	C
Lopinavir/r + Indinavir	Lopinavir ↔	Indinavir ↔	N
Lopinavir/r + Atazanavir	Lopinavir ↔	Atazanavir ↔	N
Saquinavir/r + Atazanavir	Saquinavir ↑	Atazanavir ↔	N
Saquinavir/r + Fosamprenavir	Saquinavir ↓	Fosamprenavir ↔	D
Tipranavir/r + Lopinavir, Saquinavir or Amprenavir	Lopinavir, Saquinavir, Amprenavir ↓	Tipranavir ↔	C
Lopinavir/r + Nevirapine	Lopinavir ↓	Nevirapine ↔	D
Lopinavir/r + Efavirenz	Lopinavir ↓	Efavirenz ↔	D
Saquinavir/r + Efavirenz	Saquinavir ↔	Efavirenz ↔	N
Atazanavir/r + Efavirenz	Atazanavir ↓	Efavirenz ↔	D

C indicates combination not recommended; D, dose adjustment needed; N, no clinically relevant interactions; r, low-dose ritonavir

Data in table compiled from multiple published sources. For full information please refer to the author's drug interaction web site www.hiv-druginteractions.org.

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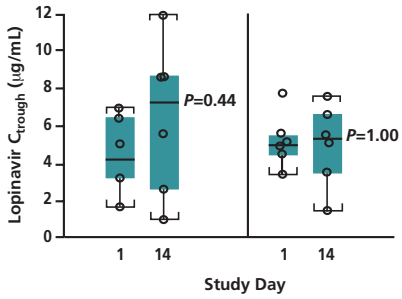

Figure **1**. Trough lopinavir concentrations in patients on lopinavir/ritonavir 400 mg/100 mg (and no other protease inhibitors or nonnucleoside reverse transcriptase inhibitors) before (day 1) and after 14 days of tipranavir 500 mg bid and either lopinavir/ritonavir 400 mg/300 mg bid (group A, left) or lopinavir/ritonavir 533 mg/233 mg bid (group B, right). Adapted from data in Harris et al, CROI, 2006.

Table **2**. Effect of Boosted Protease Inhibitors on Area Under the Curve (AUC) of Other Drugs*

	Change in AUC in presence of:		
Drug	**Lopinavir/r**	**Tipranavir/r**	**Atazanavir/r (Atazanavir)**
Rifabutin	↑3-fold	↑3-fold	(↑2.5-fold)
Atorvastatin	↑5.9-fold	↑9.4-fold	NR
Tenofovir	↑30%	↑20%	↑45%
Clarithromycin	77%	↑20%	(↑94%)
Abacavir	NR↔	↓40%	(↔)
Zidovudine	NR ↔	↓35%	(↔)
Acid Reducing Agents	↔	↓30%	↓80%
Ethinylestradiol	↓42%	↓45%	(↑48%)
Methadone	↓42%	↓50%	(↔)
Loperamide	NR↓	↓50%	↔

*Acid-reducing agent effect on protease inhibitors. NR, not reported; r, low-dose ritonavir.

Data in table compiled from multiple published sources. For full information please refer to the author's drug interaction web site www.hiv-druginteractions.org.

the effect of tipranavir. As an inhibitor of CYP3A4, tipranavir/r increases rifabutin area under the concentration-time curve (AUC) 2.9-fold, increases the AUC of the rifabutin active metabolite 20-fold, and increases atorvastatin AUC 9-fold (van Heeswijk, ICAAC, 2004; van Heeswijk et al, International Workshop on Clinical Pharmacology in HIV Therapy, 2004). Given the numerous potential drug interactions with tipranavir/r, it should be used with caution when its potential effects in combination are not known.

Effects of tipranavir/r and other boosted PIs on AUCs of other commonly used drugs are shown in Table 2; similar effects among the PIs are highlighted. Differences include the effects of acid-reducing agents on the levels of PIs. It is of interest that the increased AUC of the nucleotide analogue reverse transcriptase inhibitor (ntRTI) tenofovir with boosted PIs was an unexpected effect, with the mechanism remaining unclear. Increases in tenofovir AUC or trough concentrations have been observed with saquinavir/r and the PI darunavir (TMC 114; approved by the US Food and Drug Administration in June 2006)/r, but fosamprenavir/r does not appear to affect tenofovir trough levels. The clinical relevance of the increase in tenofovir exposure, and of the apparent differences in effect in this regard among PIs, also remains unclear.

In relation to combinations of tipranavir/r with NNRTIs, available data indicate no significant interactions with efavirenz or nevirapine. However, a recent study of tipranavir/r in combination with the investigational NNRTI etravirine (TMC125) in volunteers showed that etravirine exposure was reduced by 76% and tipranavir and ritonavir exposures were increased by 18% and 23%, respectively (Scholler et al, CROI, 2006). These findings suggest that etravirine and tipranavir/r should not be used together.

With regard to some newer agents, the PI darunavir does not appear to have clinically relevant interactions with atazanavir, tenofovir, omeprazole, or ranitidine, but does exhibit a significant interaction with atorvastatin that requires dose modification. (See Table 3.) A study of darunavir and etravirine in combination in HIV-infected subjects with 3-class antiretroviral drug resistance showed no significant pharmacokinetic interaction between the 2 (Boffito et al, CROI, 2006). The investigational CCR5 antagonist maraviroc (UK427,857) is metabolized via CYP3A4. The maraviroc AUC is increased 4.9-fold with atazanavir/r (3.6-fold with atazanavir), 3.8-fold with lopinavir/r, 2.5-fold with lopinavir/r plus efavirenz, 8.3-fold with saquinavir/r (4.3-fold with saquinavir), 5-fold with saquinavir/r plus efavirenz, 2.6-fold with ritonavir, and 5-fold with ketoconazole. The maraviroc AUC is

Table **3**. Drug Interactions with the Protease Inhibitor Darunavir

Drug Concentration		**Comment**
Atazanavir ↔	Darunavir ↔	N
Tenofovir 22%↑	Darunavir 21% ↑	N
Atorvastatin Marked Interaction	Darunavir No Data	D
Omeprazole	Darunavir ↔	N
Ranitidine	Darunavir ↔	N

D indicates dose adjustment needed; N, no clinically relevant interactions

Data in table compiled from multiple published sources. For full information please refer to the author's drug interaction web site www.hiv-druginteractions.org.

Table **4**. Effects of Various Boosting Agents on Saquinavir, Amprenavir, and Indinavir

	Change in AUC in presence of:		
Boosting Agent	**Saquinavir**	**Amprenavir**	**Indinavir**
Cimetidine	120%↑	ND	↔
Grapefruit juice	50%↑	↔	↔
Ketoconazole	70%↑	31%↑	62%↑
Itraconazole	28%↑	ND	↔
Fluconazole	50%↑	ND	25%↓
Clarithromycin	187%↑	18%↑	20%↑
Erythromycin	100%↑	ND	ND
Delavirdine	120%↑	300%↑	70%↑
Atazanavir	*	80%	ND
Ritonavir	400%-1000%↑	100%-200%↑	270%-400%↑

*Atazanavir 400 mg gives up to 50% of the boost given by ritonavir 100 mg. ND indicates no data.
Data in table compiled from multiple published sources. For full information please refer to the author's drug interaction web site www.hiv-druginteractions.org.

decreased by 50% with efavirenz alone and by 70% with rifampicin. No change in maraviroc exposure has been observed with coadministration with nevirapine or tipranavir/r.

Is There An Alternative To Ritonavir For PI Boosting?

None of the other drugs that have been examined as potential PI boosters provides the same magnitude of effect as ritonavir (Table 4). The potential for atazanavir boosting of saquinavir was recently assessed in a crossover trial in which healthy subjects received twice-daily saquinavir/r 1000 mg/100 mg, saquinavir/atazanavir 1000 mg/200 mg, or saquinavir/atazanavir 1500 mg/200 mg (King et al, CROI, 2006). Saquinavir concentrations over 12 hours following dosing on day 10 were markedly higher with ritonavir 100 mg than with atazanavir boosting (Figure 2); it was also found that saquinavir concentrations at the higher atazanavir-boosted saquinavir dose were lower than those at the lower atazanavir-boosted saquinavir dose. Another recently reported crossover trial assessed atazanavir 400 mg, fosamprenavir 1400 mg, and the combination in 21 HIV-seronegative subjects (Clay et al, CROI, 2006). When the drugs were given alone, AUCs were 17.9 μg.h/mL and 21.7 μg.h/mL for atazanavir and amprenavir, respectively, compared with 11.9 μg.h/mL (33% decrease) for atazanavir and 38 μg.h/mL (78% increase) for amprenavir when the drugs were given together. Combined treatment decreased atazanavir minimum concentrations by 0.06 μg/mL to 0.14 μg/mL and increased amprenavir minimum concentrations by 0.06 μg/mL to 0.23 μg/mL.

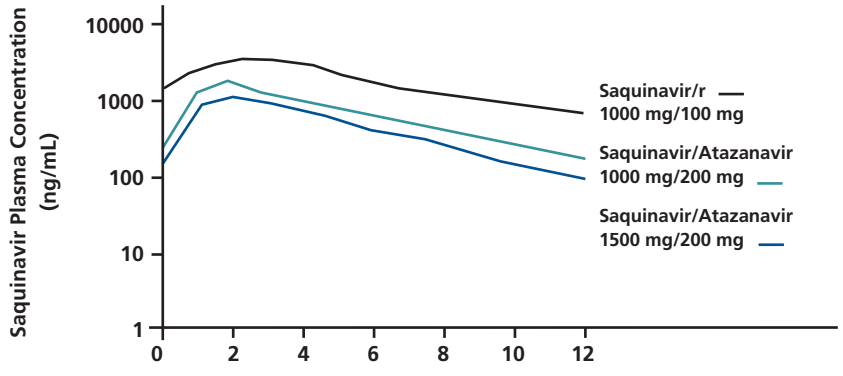

Figure **2**. 12-hour concentrations on day 10 of bid dosing of ritonavir-booster (r) saquinavir or saquinavir/atazanavir at mg doses shown in HIV-seronegative subjects. Adapted from data in King et al, CROI, 2006.

Other Important Interactions

Acid-Reducing Agents

Interactions between acid-reducing agents (ARAs) and PIs are shown in Table 5. It should be noted that there may be differences in potency among agents within each class of ARA that can result in different magnitudes of effect on PI exposure. Concomitant use of proton pump inhibitors and indinavir should be avoided. There are data suggesting that concomitant use of atazanavir and H2 blockers is possible if dosing of the 2 agents is separated by 10 hours. The clinical significance of decreased tipranavir exposure, decreased fosamprenavir exposure, and increased saquinavir exposure with concomitant ARA use currently is uncertain. Further information on ARA interactions with antiretroviral drugs is needed, with attention given to coadministration versus staggered administration, interactions in HIV-infected patients (in addition to HIV-uninfected subjects), effects of different dose levels of individual ARAs, and potential clinical consequences of any identified pharmacokinetic interactions.

Fluticasone

The potent locally-acting glucocorticoid fluticasone is rapidly metabolized via CYP3A4 after oral dosing. Coadministration with ritonavir or other CYP3A4 inhibitors, however, raises the potential for markedly increased systemic exposure and a marked decrease in endogenous cortisol levels. Consequences can include systemic effects such as adrenal sup-

Table 5. Effects of Acid-Reducing Agents on Protease Inhibitors

Protease Inhibitor	Antacids	H_2 Blockers	Proton Pump Inhibitors	Significance
Saquinavir/r (1000/100 mg bid)		C_{12} ↑ AUC ↑	C_{12} AUC 80%	Unclear
Indinavir (800 mg tid)			C_{min} 55% AUC 46.7%	+++
Lopinavir/r (400 mg/100 mg bid)	↔	↔	↔	Unlikely
Fosamprenavir (1400 mg bid)	C_{min} ↑14% AUC ↓18%	C_{min} ↔ AUC ↓30%	↔	Possible
Fosamprenavir/r (700 mg/100 mg bid)			↔	
Atazanavir/r (400 mg qd)		C_{min} ↓42% AUC ↓41%	C_{min} and AUC ↓80%	+++ (Separate if H_2 blocker)
Atazanavir/r (300 mg /100 mg qd)		C_{min} ↓28% AUC ↓18%	C_{min} and AUC ↓70%	+++ (Separate if H_2 blocker)
Tipranavir/r (500 mg/200 mg bid)	C_{min} ↓29% AUC ↓27%			Possible
Darunavir/r (400 mg/100 mg bid)		↔	↔	Unlikely

AUC indicates area under the concentration-time curve; bid, twice daily; C_{12}, concentration at end of 12-hour dosing interval; H_2 blocker, histamine H2 receptor antagonist; C_{min}, minimum concentration; qd, daily; tid, thrice daily. Data in table compiled from multiple published sources. For full information please refer to the author's drug interaction web site www.hiv-druginteractions.org.

pression and Cushing's syndrome.

Methadone and Buprenorphine

As listed in Table 6, available data indicate that most PIs and the NNRTIs efavirenz and nevirapine reduce morphine levels. Although there are few substantive data in this regard, buprenorphine levels are believed to be increased by PIs and reduced by efavirenz and nevirapine.

Table 6. Interactions Between Antiretroviral Drugs and Methadone or Buprenorphine

	Methadone	Buprenorphine
Atazanavir	↔	?↑
Fosamprenavir	13% ↓	?↑
Indinavir	↔	?↑
Lopinavir/r	30%-50%↓	?↑
Nelfinavir	47%↓	?
Saquinavir	32%↓	?↑
Tipranavir	50%↓	?↑
Efavirenz	52%↓	50%↓
Nevirapine	46%↓	?↓

Data in table compiled from multiple published sources. For full information please refer to the author's drug interaction web site www.hiv-druginteractions.org.

CYP Genomics

Differences in genes regulating CYP enzymes can have significant effects on drug metabolism and exposure. For example, 1 study of polymorphisms at the 516 position of the CYP2B6 gene has shown that individuals with the 516T/T variant have a 3-fold increase in efavirenz concentrations and markedly increased efavirenz AUC compared with individuals with wild-type 516G/G or the 516T/G variant (Haas et al, *AIDS*, 2004). Data from a study in the Swiss HIV Cohort indicate that most patients with very high efavirenz concentrations on standard doses, some of whom had central nervous system (CNS)-related toxicity, had single nucleotide polymorphisms in the CYP2B6 gene at both the 516 and 785 positions. In the case of efavirenz, and other drugs for which pharmacogenomic data are accumulating, it is unclear at present whether genotypic testing or TDM should be used to guide dosing. It is likely that most genotypic and phenotypic relationships affecting drug metabolism and exposure reflect the involvement of numerous genes and numerous polymorphisms. As more information in this regard is gained, genotypic testing is likely to be an increasingly used tool in both selecting antiretroviral agents and achieving optimal dosing.

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Suggested Reading

Boffito M, Winston A, Fletcher C, et al. Pharmacokinetics and ART response to TMC114/r and TMC125 combination in patients with high-level viral resistance. [Abstract 575C.] 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006; Denver, Colorado.

Clay P, Anderson P, Smith P, Lein D, Glaros A. Pharmacokinetics of once-daily fosamprenavir 1400 mg plus atazanavir 400 mg without ritonavir in HIV-negative subjects. [Abstract 587.] 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006; Denver, Colorado.

Harris M, Ramirez S, Joy R, et al. Effect of lopinavir and ritonavir dose adjustments on the pharmacokinetic interaction between LPV/RTV and tipranavir. [Abstract 584.] 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006; Denver, Colorado.

King J, Paul Lundy S, Kakuda T, Becker S, Acosta E. Pharmacokinetics of saquinavir with low-dose ritonavir or atazanavir twice daily in seronegative volunteers: ASPIRE II.

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van Heeswijk R, Sabo J, MacGregor T, et al. The pharmacokinetic (PK) interaction between single-dose rifabutin (RFB) and steady-state tipranavir/ritonavir 500/200 mg bid (TPV/r) in healthy volunteers. [Abstract A-456.] 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. October 30-November 2, 2004; Washington, DC.

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