Perspective

Drug-Drug Interactions With Newer Antiretroviral Agents

Knowledge of drug interactions among antiretroviral agents and other drugs used by HIV-infected patients is essential to maintaining safety and efficacy of drug treatment. Often, the clinical impact of drug-drug interactions cannot be predicted on the basis of pharmacokinetic interactions alone, highlighting the need for studies and analyses that provide exposure-response data. Drug interactions in HIV-infected patients can be complex and sometimes counterintuitive, and practitioners must increasingly rely on a concerted approach to gathering information on drug interactions that goes beyond studies showing exposure changes for coadministered drugs. This article summarizes a presentation on drug-drug interactions of newer antiretroviral agents made by Judith A. Aberg, MD, at the 11th Annual Clinical Update for the Ryan White HIV/AIDS Program Clinicians held in August 2008 in Washington, DC. The original presentation is available as a Webcast at www.iasusa.org

Information on drug-drug interactions involving antiretroviral agents and other drugs used by HIV-infected patients is confusing. To understand the interactions and how they affect clinical practice, it is necessary to have a grasp of the basic concepts and terminology involved in assessing drug behavior. *Pharmacokinetics* is the mathematics of the time course of absorption, distribution, metabolism, and excretion of drugs in the body. *Pharmacodynamics* refers to relationships between the dose or concentration of a drug in the body (exposure) and the measured effects of the drug. *Pharmacogenomics* refers to the entire spectrum of genes that determine drug efficacy and safety, whereas *pharmacogenetics* concerns distinct inherited traits related to drug absorption, disposition, and response. Inducers of enzymes (or transporters) that metabolize drugs are agents that stimulate production of enzymes and thus decrease levels of the substrate; rifampin, nevirapine, and efavirenz are examples of inducers. *Inhibitors* are agents that inhibit production of enzymes (or transporters) responsible for metabolism and thus act to increase levels of substrate; ritonavir is an example of a potent inhibitor.

Much of the discussion about inducers and inhibitors concerns the interaction of drugs with cytochrome P450 (CYP) enzymes. These enzymes reside primarily in the liver and gut mucosa (and at lower levels in the lungs, kidney, and brain). Six isoenzymes account for the metabolism of nearly half of all clinically used drugs (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A3, and CYP3A4). Patients may have genetic variants of CYP enzymes that affect their metabolic activity such that the activity can be classified according to each patient's phenotype as "poor," "intermediate," "extensive," or "ultrarapid"/"ultraextensive." Drug interactions occur when the pharmacokinetics or pharmacodynamics of 1 drug is altered by another. These interactions are a source of variability in drug responses, which can differ according to concentrations of the interacting drugs, dose, and time. Pharmacokinetic interactions can affect absorption rate, availability, distribution, and hepatic or renal clearance. Pharmacodynamic interactions can be antagonistic, additive, or synergistic.

Case 1: Ineffective Pain Control

A 46-year-old African American man, doing well on antiretroviral therapy with tenofovir, emtricitabine, and ritonavir-boosted (/r) fosamprenavir, presents 1 day after falling off a motorcycle and receiving sutures for lacerations and treatment for arm and leg pain at the emergency department. He states that he is unable to sleep or concentrate at work because of the pain, which was not responsive to ibuprofen. Examination shows multiple abrasions and contusions. He is prescribed acetaminophen with codeine, after reporting a history of using codeine years before with no adverse effects. He calls the office 2 days later and states that he has been vomiting and feels "sick" all day. He denies having a fever or eating any new foods since the accident and states that the codeine did not relieve the pain.

The likely explanation for these symptoms concerns interactions with codeine, which is a prodrug and substrate of CYP2D6 that requires metabolism to its active metabolite (morphine) to provide pain relief. In an individual who has inhibited catabolism, codeine levels will accumulate, causing gastrointestinal toxicity without pain relief. The patient had no history of adverse events the last time he took codeine; however, he is now receiving ritonavir, a CYP2D6 inhibitor. The CYP2D6 inhibition reduces codeine metabolism, thereby raising codeine levels and producing codeine toxicity with no pain relief.

Drug Interactions: Not So Simple

Many of the potential drug interactions in HIV-infected patients are not as readily identified as that between ritonavir and codeine in the patient described above. Understanding drug interactions is crucial to making accurate benefit-risk assessments in HIV patients, but these interactions can be complex and, at times, counterintuitive. Drugs may serve as substrates, inducers, or inhibitors of drug-metabolizing enzymes and transporters, and the complexity of drug metabolism when several medications are prescribed makes predicting interactions nearly impossible. The clinical importance of interactions can-

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not be determined solely on the basis of the reported magnitude of changes in drug plasma concentrations.

Increasingly, practitioners must rely on a concerted approach to gathering information on drug interactions that goes beyond the studies showing changes in exposure for 2 coadministered drugs. To this end, several principles of drug-interaction studies should be observed (Huang et al, *Clin Pharmacol Ther*, 2007): (1) An in vitro and in vivo integrated approach may reduce the number of studies required to detail interactions and optimize knowledge of interactions. (2) Appropriately designed studies of interactions are crucial to reaching the clinical goal of avoiding potentially harmful interactions in patients receiving numerous drugs simultaneously. (3) The clinical importance of interactions should be based on clinical trial data and well-defined exposure-response data and analyses. (4) Classification of CYP inhibitors and substrates can aid in study design and cross-labeling. (5) Information on drug interactions should be placed appropriately in drug labeling.

Case 2: Etravirine and Darunavir

A 21-year-old man with vertically acquired HIV has resistance to several nucleoside analogue reverse transcriptase inhibitors (nRTIs), the K103N nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance mutation, and several protease inhibitor (PI) resistance mutations. Results of coreceptor tropism testing show a dual or mixed profile. Phenotypic analysis indicates that darunavir, lopinavir/r, and tipranavir should be active, with reduced activity of atazanavir and fosamprenavir. It is decided to prescribe the integrase inhibitor raltegravir, the NNRTI etravirine, and a ritonavir-boosted PI. The choice of PI from among darunavir, lopinavir, tipranavir, atazanavir, or fosamprenavir requires clinical judgment regarding which drug would provide the most potency, tolerability, and ability to be coadministered with other active agents.

A look at etravirine interactions with PIs narrows the selection. The effects of ritonavir-boosted PIs on etravirine maximum concentration (C_{max}), area under the curve (AUC), and minimum concentration (C_{min}) and the effects of etravirine on ritonavir-boosted-PI exposure are shown in Table 1. Etravirine exposure is reduced by darunavir/r but reduced more by tipranavir/r, whereas exposure is increased somewhat with lopinavir/r and increased to a greater extent with atazanavir/r. For the PIs, etravirine coadministration results in a marked decrease in atazanavir C_{min} value and a marked increase in exposure to fosamprenavir, with minimal to moderate effects on exposure to darunavir and lopinavir.

Recommendations from the etravirine package insert are summarized in Table 2. Coadministration of atazanavir/r or tipranavir/r is not recommended because of the decreased PI exposure, and use of fosamprenavir/r is not recommended because of increased fosamprenavir exposure. Although the etravirine C_{min} value is reduced by approximately 50% with darunavir/r, coadministration without dose adjustment can still be recommended on the basis of clinical findings in the DUET studies indicating reduction in plasma HIV RNA level to less than 50 copies/mL in 59% of patients receiving the 2 drugs (Lazzarin et al, *Lancet*, 2007; Madruga et al, *Lancet*, 2007).

This finding provides an example of a situation in which the clinical importance of the drug interaction does not appear to be predictable from data on the pharmacokinetic interaction alone, emphasizing the utility of clinical trial or exposure-response data in clinical decision-making. Similarly, although etravirine exposure is increased with coadministered lopinavir/r, data from a clinical trial population have suggested that coadministration is safe, with the current recommendation being that etravirine and lopinavir/r can be coadministered with caution.

Case 3: Coinfection With Tuberculosis

A 36-year-old woman who received a diagnosis of HIV 6 years ago presents

Table **1.** Etravirine and Protease Inhibitor (PI) Interactions

	Maximum Concentration	Area Under the Curve	Minimum Concentration
Effect of PI on etravirine: Ratio in presence of PI (1.00 = no effect)			
Atazanavir/r 300 mg/100 mg, daily	1.30	1.30	1.26
Darunavir/r 600 mg/100 mg, twice daily	0.68	0.63	0.51
Lopinavir/r 400 mg/100 mg, soft gel capsule, twice daily	1.15	1.17	1.23
Tipranavir/r 500 mg/200 mg, twice daily	0.29	0.24	0.18
Effect of etravirine on PI: Ratio in presence of etravirine (1.00 = no effect)			
Atazanavir/r 300 mg/100 mg, twice daily	0.97	0.86	0.62
Darunavir/r 600 mg/100 mg, twice daily	1.11	1.15	1.02
Lopinavir/r 400 mg/100 mg, soft gel capsule, twice daily	0.85	0.80	0.92
Fosamprenavir/r 700 mg/100 mg, twice daily	1.62	1.69	1.77

/r indicates ritonavir-boosted.
Adapted from etravirine package insert, 2008.

Table **2.** Recommendations for Etravirine Coadministration with Protease Inhibitors

Protease Inhibitor	Recommendation for Etravirine Coadministration
Atazanavir/ritonavir	Should NOT be coadministered; atazanavir exposure decreased by 38%
Darunavir/ritonavir	May be coadministered without dose adjustment; recommendation based on DUET study (etravirine exposure decreased by 50%, yet 59% vs 41% had plasma HIV RNA level < 50 copies/mL)
Lopinavir/ritonavir	Etravirine exposure may be increased by 85% in HIV-infected patients; may be coadministered with caution
Fosamprenavir/ritonavir	Should NOT be coadministered; fosamprenavir exposure increased by 77%
Tipranavir/ritonavir	Should NOT be coadministered; etravirine exposure decreased by 75%

Adapted from etravirine package insert, 2008.

with pulmonary tuberculosis. She has a history of nonadherence to medications. Prior genotypic testing indicated M184V, K103N in reverse transcriptase, and 2 minor PI resistance mutations. She is started on 4-drug therapy for tuberculosis with isoniazid, rifampin, pyrazinamide, and ethambutol, tolerating treatment well for 3 weeks, and agrees to start antiretroviral therapy.

What would be the best antiretroviral therapy option? Possibilities include (1) nRTI plus efavirenz and change rifampin to rifabutin 300 mg/day; (2) nRTI plus etravirine and change rifampin to rifabutin 300 mg/day; (3) nRTI plus any ritonavir-boosted PI and continue rifampin as prescribed; or (4) nRTI plus etravirine plus ritonavir-boosted PI and change rifabutin dosage to 150 mg every other day.

The best choice would be option 2. For option 1, the dose of rifabutin would have to be increased to 450 mg/day if it were used with efavirenz. Of note, in this particular case, the patient has a K103N mutation, which confers resistance to efavirenz, so efavirenz is not an option for this patient. Option 3 is not correct because rifampin cannot be used with a PI. A summary of etravirine drug interactions (Table 3) reveals that choices of ritonavir-boosted PIs that can be administered with etravirine are limited. For those that can be coadministered, use is not recommended with rifabutin because of the potential for substantial reductions in etravirine exposure; thus, option 4 is not correct. If no boosted PI is used in this patient's regimen, neither the dose of rifabutin nor that of etravirine needs to be altered.

Ritonavir-boosted darunavir is among the few PI options for coadministration with etravirine. As for other PIs, coadministration with rifabutin affects rifabutin exposure, requiring dose adjustment. However, as a caution against assuming class effects in drug interactions, note that unlike for other PIs, darunavir/r increases, rather than reduces, levels of pravastatin. Pravastatin is metabolized mainly by glucuronidation. The mechanism of the interaction of darunavir/r with pravastatin remains unclear, although it may involve effects on drug-transporter proteins. The darunavir package insert recommends starting with the lowest possible dose of pravastatin with careful monitoring when coadministered with darunavir/r or to consider an alternative statin (darunavir package insert, 2008).

Raltegravir

Raltegravir is not a CYP substrate. Based on in vitro and in vivo studies, it appears to be eliminated mainly by metabolism via a glucuronidation pathway mediated by uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1). Rifampin is a strong inducer of UGT1A1 and reduces raltegravir trough levels (concentration at 12 hours, C_{12h}) by 61%, consistent with a clinically meaningful reduction (mean AUC and C_{max} values reduced by 40% and 38%, respectively). Currently, the effect of other inducers of drug-metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Raltegravir exposure is reduced with coadministered efavirenz (AUC ratio, 0.64; C_{12h} ratio, 0.79) (Iwamoto et al, ICAAC, 2006) and tipranavir/r (AUC ratio, 0.76; C_{12h} ratio, 0.45) (Wenning et al, ICAAC, 2006) and increased with atazanavir/r (AUC ratio, 1.41; C_{12h} ratio, 1.77) (Mistry et al, CROI, 2006), but no dosing changes for any of these drugs are currently recommended with coadministration.

Despite the reduced raltegravir exposure with tipranavir/r, efficacy in approximately 100 patients receiving the 2 drugs in 2 trials (protocols 018 and 019) was similar to that in patients receiving non–tipranavir/r (Steigbigel et al, *N Engl J Med*, 2008). Although atazanavir/r is a strong inhibitor of UGT1A1 and increases raltegravir exposure, concomitant use was safe and effective in patients in 3 trials (protocols 005, 018, and 019) (Steigbigel et al, *N Engl J Med*, 2008; Grinsztejn et al, *Lancet*, 2007).

Maraviroc

The CC chemokine receptor 5 (CCR5) antagonist maraviroc is a substrate for both CYP3A isoenzymes and the P-glycoprotein transporter. A 50% dose reduction for maraviroc is recommended when it is coadministered with most PIs. Because the combined use of maraviroc and tipranavir/r is desirable in heavily treatment-experienced patients, a randomized, open-label, 2-way crossover trial in 12 healthy volunteers was performed to evaluate the pharmacokinetic interaction of maraviroc 150 mg twice daily with tipranavir/r (500/200 mg) (Abel et al, *Br J Clin Pharmacol*, 2008). Coadministration had no effect on maraviroc concentrations compared with maraviroc

Table 3. Coadministration and Dosing Considerations for Etravirine

No Dose Adjustment of Etravirine or Coadministered Drug	
Darunavir/ritonavir	Methadone
Saquinavir/ritonavir	Rifabutin (unless combined with ritonavir-boosted protease inhibitor)[b]
Tenofovir	Oral contraceptives
Didanosine	Paroxetine
Raltegravir	Clarithromycin (alternative should be considered for treatment of *Mycobacterium avium* complex)
Elvitegravir/ritonavir[a]	
Omeprazole	
Ranitidine	
Coadminister with Caution	
Lopinavir/ritonavir	
Modify Dose of Coadministered Drug	
Sildenafil (alter based on clinical effect)	Maraviroc (modify dose)
Atorvastatin (alter based on clinical effect)	
Do Not Coadminister	
Tipranavir/ritonavir	Delavirdine
Atazanavir/ritonavir	Nevirapine
Fosamprenavir/ritonavir	Efavirenz
Full-dose ritonavir	
Protease inhibitors without ritonavir	
Atazanavir	Indinavir
Fosamprenavir	Nelfinavir

[a]Ramanathan et al, ICAAC, 2007.
[b]If etravirine is *not* coadministered with a ritonvair-boosted (/r) protease inhibitor, use rifabutin at a dosage of 300 mg once daily; if etravirine is coadministered with darunavir/r or saquinavir/r, rifabutin should not be coadministered because of potential for substantial reductions in etravirine exposure.
Adapted from etravirine package insert, 2008.

plus placebo, with 5 patients having increased levels of liver enzymes.

The absence of effect on maraviroc concentrations indicates that the effects of CYP inhibition and P-glycoprotein induction balanced each other, and that the recommended maraviroc dose does not need to be altered with concomitant tipranavir/r. Available data on effects of coadministration of maraviroc with antiretroviral combinations indicate reduced maraviroc exposure with a regimen of efavirenz, zidovudine, and lamivudine (C_{max}, −33%; AUC, −53%), reduced exposure with a regimen of efavirenz, didanosine, and tenofovir (C_{max}, −24%; AUC, −52%), increased peak concentrations with a regimen of nevirapine, lamivudine, and tenofovir (C_{max}, +54%; AUC, no change), and increased exposure with a regimen of lopinavir/r, stavudine, and lamivudine (C_{max}, +180%; AUC, +265%) (Muirhead et al, CROI, 2005; Abel et al, *Br J Clin Pharmacol*, 2008).

A further example of competing interactions arises with the use of maraviroc with efavirenz and PIs that increase maraviroc exposure by inhibiting CYP3A4. Maraviroc exposure (as measured by C_{max} and AUC values) is reduced with the known CYP3A4 inducers rifampicin and efavirenz by approximately 70% and 50%, respectively. The addition of efavirenz to maraviroc-plus-PI regimens reduces the magnitude of the PI-mediated increase in maraviroc exposure (by approximately 50%), with the net effect still being CYP3A4 inhibition (Abel et al, *Br J Clin Pharmacol*, 2008). Thus, a dose reduction for maraviroc is needed in this situation.

Overall, based on data from clinical trials, exposure-response information, the drug interaction program, and population pharmacokinetics analysis in phase IIb/III trials, the recommended dosing for maraviroc is:

- 150 mg twice daily when used with PIs, excluding tipranavir/r, and delavirdine
- 300 mg twice daily when used with tipranavir/r, nRTIs, enfuvirtide, or nevirapine
- 600 mg twice daily when used with efavirenz in the absence of PIs

Additional Information Sources

Because some clinically important drug interactions are counterintuitive or seem inconsistent with assumed class effects, HIV practitioners should consult the drug interaction sections of prescribing information for antiretroviral drugs. The following are additional antiretroviral drug interaction resources:

- **www.hivinsite.com:** Updated drug interaction database with references and interactive tool to assess drug interactions.
- **www.aidsinfo.nih.gov:** US Department of Health and Human Services guidelines for use of antiretroviral agents and updated drug interaction tables.
- **www.drug-interactions.com:** Downloadable drug interaction charts; interactive tools to assess interactions; updated news on published abstracts and papers.
- **www.hivmedicationguide.com:** Interactive drug interaction database.
- **www.hivpharmacology.com:** Updated summary of drug interaction data; guidelines for therapeutic drug monitoring.
- Micromedex: Comprehensive drug database; subscription required.

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