

Polypharmacy Problems: Drug Interactions In the Multidrug Therapy of HIV Infection

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PATIENTS WITH HIV RECEIVE AN ABUNDANCE of daily medications, often including a triple-drug antiretroviral regimen, primary and/or secondary prophylactic drugs, and other compounds as needed (e.g., lipid-lowering drugs). Clinicians will be the first to admit that the proper use of these drugs has yielded highly desirable effects—including prolonged survival and fewer opportunistic infections—but will also attest to the burgeoning task of monitoring possible drug interactions.

Of course, the risk of harmful interactions does not stop with the pharmacokinetic profiles of individual drugs. Clinicians must also remain aware of possible interactions between the drugs they prescribe and such things as foods, other diseases, and nontraditional agents such as vitamins, herbal remedies, and an often unacknowledged factor: recreational drugs.

Taking all of these possible interactions into account, one retrospective chart review of 50 patients with HIV demonstrated a substantially increased likelihood of drug interactions with the addition of a single new drug—a protease inhibitor—to their therapeutic regimens. Upon adding the protease inhibitor, the probability of at least one undesirable drug interaction was 31%, 42%, and 77% for patients treated with indinavir, saquinavir, and ritonavir, respectively, across all CD4+ cell counts. For the cohort with CD4+ counts below 100 cells/mm³ the probability jumped to 55%, 63%, and 93%, respectively (Barry, 1997).

According to Dr. Pau—who began her PRN lecture with a mind-boggling, yet all-too-common case report involving an HIV-positive man receiving a total of 16 drugs for the treatment of HIV, tuberculosis, hepatitis C, hyperlipidemia—there is a dire

need for clinicians and other health-care providers to understand the potential for drug interactions and to critically evaluate their patients' current drug regimens before adding new agents.

Mechanisms of Drug Interactions

DRUGS INTERACT IN TWO MAJOR WAYS: PHARMACOKINETICALLY and pharmacodynamically. A pharmacokinetic drug interaction occurs when one drug causes a change in another drug's serum concentration by altering its absorption, distribution, metabolism, or elimination. A pharmacodynamic drug interaction occurs when the clinical effect is altered by administering the two drugs concomitantly, such as those yielding synergistic or antagonistic therapeutic effects and those yielding overlapping or additive toxicities. A prime example of a pharmacodynamic interaction is the positive synergistic antiviral effect of zidovudine (Retrovir)/lamivudine (EpiVir) coadministration. On the flip side, a negative pharmacodynamic effect might occur when two drugs known to cause either bone marrow suppression (e.g., zidovudine and ganciclovir [Cytovene]), nephrotoxicity (e.g., didanosine [Videx] and amphotericin B [Fungizone]), or neuropathy (e.g., stavudine [Zerit] and didanosine [Videx; Videx EC]) are combined.

In terms of potential pharmacokinetic interactions, numerous possibilities abound. For starters, there are interactions that can affect drug absorption. Some of the possible mechanisms by which this can occur include alterations in gastric pH, chelation of compounds, gastric emptying, intestinal motility, intestinal blood flow, intestinal CYP3A4 activities, and intestinal P-glycoprotein activities.

Using gastric pH as an example, Dr. Pau explained that, when one drug alters acidity in the gut, the dissolution of another concomitantly administered pH-dependent drug may be affected, thereby diminishing its absorption. Two classic cases in point are ketoconazole (Nizoral), which requires an acidic gastric environment for solubilization, and didanosine, which requires high gastric pH for stability. As the didanosine tablet, powder, and suspension formulations contain an antacid buffer, coadministration of these two drugs would result in poor absorption of ketoconazole.

Similarly, clinicians need to recognize that the intestine also plays a significant role in the absorption and metabolism of certain oral medications. As described in "Pharmacology to the Fore," an article summarizing a lecture delivered by David Back, PhD, in the June 2001 issue of *The PRN Notebook*, cells within the intestinal wall contain cytochrome P450 enzymes and influx/efflux transporters, such as P-glycoprotein, which can greatly reduce drug levels even before they reach the liver for additional metabolizing. Conversely, drugs that affect intestinal cytochrome P450 and P-glycoprotein activities may result in positive pharmacokinetic interactions. A typical example is the coadministration of ritonavir and saquinavir, resulting in a significant boost in the bioavailability of the latter agent.

Dr. Pau also noted other factors that can influence pharmacokinetics and increase the risk of drug-drug interactions. These include age; gender; race, which is associated with various genetic polymorphisms in certain P450 enzymes (e.g., approximately 5% to 10% of Caucasians and 1% to 3% of African Americans and Asians lack functional CYP2D6 enzyme); body size

TABLE 1. Interactions to Watch For: Antiretrovirals and Lipid-Lowering Agents						
Protease Inhibitors	Amprenavir	Indinavir	Lopinavir	Nelfinavir	Ritonavir	Saquinavir
Atorvastatin	■	■	■	■	■	■
Cerivastatin	■	■	■	■	■	■
Clofibrate	▲	▲	▲	▲	▲	▲
Fenofibrate	▲	▲	▲	▲	▲	▲
Fluvastatin	■	■	■	■	■	■
Gemfibrozil	▲	▲	▲	▲	▲	▲
Lovastatin	■	✗	✗	✗	✗	✗
Pravastatin	▲	▲	▲	▲	▲	▲
Simvastatin	■	✗	✗	✗	✗	✗
Non-Nucleoside Reverse Transcriptase Inhibitors	Delavirdine	Efavirenz	Nevirapine	KEY TO SYMBOLS:		
Atorvastatin	■	■	■	✗ These drugs should not be coadministered ■ Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration ▲ No clinically significant interaction		
Cerivastatin	■	■	■			
Clofibrate	▲	▲	▲			
Fenofibrate	▲	▲	▲			
Fluvastatin	■	■	■			
Gemfibrozil	▲	▲	▲			
Lovastatin	■	■	■			
Pravastatin	▲	▲	▲			
Simvastatin	■	■	■			

Source: <http://www.hiv-druginteractions.org> (January 2002 update). Adapted and reprinted with permission of the Liverpool HIV Pharmacology Group. Interactions shown are based on preliminary data presented at scientific congresses and final reports published in peer-reviewed medical journals. This and other drug-interaction tables on the Liverpool HIV Pharmacology Web site are continuously updated and are accompanied by data summaries for each possible interaction. Readers of this article are urged to consult the Liverpool HIV Pharmacology Group for the most recent updates.

and composition; concomitant conditions (e.g., pregnancy), concomitant disease states (e.g., hepatitis B, hepatitis C, and congestive heart failure); acute or chronic changes of organ function; and diet, alcohol, and tobacco use.

Ironically, factors that can affect pharmacokinetics in certain patient populations are often poorly studied in clinical trials. Dr. Pau pointed out that numerous pharmacokinetic studies of antiretroviral agents are conducted in healthy, non-HIV infected volunteers. These studies are usually brief in duration—single-dose or short multiple-dose therapy is still the norm—and have stringent inclusion/exclusion criteria, including normal organ function and no concomitant drugs or disease states.

NRTI Interactions to Watch For

WHEN IT COMES TO DRUG-DRUG INTERACTIONS, most clinicians will first call to mind the pharmacokinetics conundrum associated with the protease inhibitors. However, nucleoside reverse transcriptase inhibitors (NRTIs) are hardly innocent when it comes to drug-drug interactions and must be prescribed cautiously in light of this.

Zidovudine, perhaps the most comprehensively studied of all the NRTIs, is associated with a number of potential drug interactions. For example, probenecid (Benemid; Probalan) appears to reduce renal excretion of zidovudine, resulting in marked and prolonged concentrations of zidovudine in the blood. Similarly, concomitant administration of valproic acid (Depacon; Depakene; Depakote) and zidovu-

dine results in a significant (~79%) increase in the AUC of zidovudine and a decrease (~20%) in the AUC of its glucuronide metabolite, GZDV. The reason for this is not entirely understood, although it has been suggested that valproic acid may inhibit glucuronidation of zidovudine.

Some antivirals commonly used by HIV-positive people can also make for a messy pharmacokinetic mix with zidovudine. First, zidovudine combined with stavudine can have an antagonistic effect. This likely occurs because of competition for cellular thymidine kinase that is needed for monophosphorylation of both drugs. Ribavirin (Rebatol) may also antagonize the antiretroviral activity of zidovudine. This antagonism appears to result from inhibition of zidovudine phosphorylation by

TABLE 2. Interactions to Watch For: Antiretrovirals and Herbal/Nutraceutical Therapies

Protease Inhibitors	Amprenavir	Indinavir	Lopinavir	Nelfinavir	Ritonavir	Saquinavir
Echinacea	✗	✗	✗	✗	✗	✗
Garlic	■	■	■	■	■	■
Grapefruit Juice	▲	▲	▲	▲	▲	▲
Milk Thistle	■	■	■	■	■	■
Seville Orange Juice	▲	▲	▲	▲	▲	▲
St John's Wort	✗	✗	✗	✗	✗	✗
Vitamin E	✗	▲	▲	▲	▲	▲

Non-Nucleoside Reverse Transcriptase Inhibitors	Delavirdine	Efavirenz	Nevirapine
Echinacea	✗	✗	✗
Garlic	■	■	■
Grapefruit Juice	▲	▲	▲
Milk Thistle	■	■	■
Seville Orange Juice	▲	▲	▲
St John's Wort	✗	✗	✗
Vitamin E	▲	▲	▲

KEY TO SYMBOLS:

- ✗ These drugs should not be coadministered
- Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration
- ▲ No clinically significant interaction

Source: <http://www.hiv-druginteractions.org> (January 2002 update). Adapted and reprinted with permission of the Liverpool HIV Pharmacology Group.

ribavirin and/or phosphorylated ribavirin, possibly secondary to a ribavirin-induced increase in deoxythymidine triphosphate (dTTP) concentrations and a subsequent feedback inhibition of thymidine kinase. While this has led to the official stance that concurrent use of zidovudine and ribavirin is contraindicated, one recent study published in *AIDS* found that coadministration did not yield any noticeable reductions in the potency and durability of HAART (Morisca, 2000).

While the bulk of zidovudine's potential interaction problems are along the lines of impaired metabolism and clearance, didanosine's tribulations begin much earlier in the pharmacokinetic chain of events. Absorption problems are usually the issue with the buffered formulations of didanosine, which results in a number of drug mixes to watch for. Didanosine can decrease absorption of itraconazole (Sporanox), ketoconazole, dapsone (Avlosulfon; DDS), and delavirdine (Rescriptor) because of increased gastric pH. It can also decrease absorption of the quinolones and the tetracyclines by chelation of these antibiotics with the magnesium and calcium

ions contained in the buffer. Turning the tables, methadone can decrease didanosine absorption, and oral ganciclovir can increase the AUC of didanosine by approximately 100%, although the reasons for this are not understood. Tenofovir DF (Viread), the newest member of the antiretroviral arsenal, can increase the AUC of didanosine by 44% and its C_{max} by 28%—the clinical significance of this particular interaction has not yet been determined. Interactions involving the new enteric-coated formulation of didanosine with other medications have not yet been fully elucidated.

NRTIs also have their share of interactions that affect pharmacodynamics of coadministered drugs. Zidovudine combined with TMP-SMX (Bactrim; Septra) or ganciclovir can increase the risk of bone marrow toxicities, including anemia and neutropenia. There is also the prevailing fear surrounding the combination of two or more of the "d" drugs—ddI (didanosine), ddC (zalcitabine; Hivid), and d4T (stavudine)—which may be associated with an increased risk of peripheral neuropathy and, perhaps, mitochondrial toxicity.

Cytochrome P450: The Good, the Bad, and the Ugly

MOST MEDICATIONS USED TO TREAT A VARIETY of diseases are cleared from the body by way of biotransformation in the liver. The primary goal of hepatic metabolism is to convert lipophilic compounds into polar metabolites, which are then excreted in urine or feces.

There are two ways in which the liver does this. The first involves cytochrome P450 enzymes, which are responsible for the oxidative metabolism of many compounds. These are known as Phase I reactions. Phase II reactions involve conjugation enzymes, which link one chemical to another. For example, glucuronyl transferases link a glucuronide group to zidovudine, which makes it more water soluble and, as a result, more easily excreted in urine.

Of particular concern to Dr. Pau is the potential for interactions between drugs that are metabolized via the cytochrome P450 system, since many antiretroviral drugs affect this system. The induction or inhibition of various P450 isoenzymes can substantially affect drug serum concen-

TABLE 3. Interactions to Watch For: Antiretrovirals and Illicit/Recreational Drugs						
Protease Inhibitors	Amprenavir	Indinavir	Lopinavir	Nelfinavir	Ritonavir	Saquinavir
Alcohol	▲	▲	▲	▲	▲	▲
Gamma-hydroxybutyrate (GHB)	▲	▲	▲	▲	■	▲
Marijuana	▲	▲	■	▲	■	▲
MDMA (“Ecstasy”)	■	■	■	■	■	■
Methamphetamine	■	■	■	■	■	■
Non-Nucleoside Reverse Transcriptase Inhibitors						
	Delavirdine	Efavirenz	Nevirapine			
Alcohol	▲	▲	▲	KEY TO SYMBOLS: ■ Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration ▲ No clinically significant interaction		
Gamma-hydroxybutyrate (GHB)	▲	▲	▲			
Marijuana	▲	▲	▲			
MDMA (“Ecstasy”)	■	▲	▲			
Methamphetamine	■	▲	▲			

Source: <http://www.hiv-druginteractions.org> (January 2002 update). Adapted and reprinted with permission of the Liverpool HIV Pharmacology Group.

trations, thereby impacting both efficacy and the risk of toxicity.

The cytochrome P450 (CYP) mixed-function monooxygenases are located on the smooth endoplasmic reticulum of cells throughout the body, primarily the liver. Some P450 isoenzymes can also be found in the lung, the kidney, the brain, the small intestine, and the placenta.

In humans, there are more than 20 different cytochrome enzymes, of which eight are responsible for the metabolism of nearly all clinically useful medications. Although these eight enzymes—CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4—are somewhat related and share many general characteristics, each is unique in its substrate specificity and thus metabolizes specific drugs. Aside from their ability to metabolize drugs, these isoenzymes are responsible for metabolizing environmental toxins, dietary components, and various endogenous substances (e.g., steroids, prostaglandins, etc.). To further complicate the issue, certain physiologic changes such as the presence of inflammation, increases in proinflammatory cytokine production (e.g., interleukin-1, interleukin-6, and tumor necrosis factor- α), and hormonal changes during pregnancy, may all contribute to changes in CYP activities.

In order to completely understand and predict cytochrome P450 drug interactions,

it is important to distinguish between the different enzymes, particularly those known to have a role in metabolizing the most commonly used medications to treat HIV and its associated manifestations. Three of the most relevant enzymes, as they relate to antiretroviral medications, are discussed here:

Cytochrome P450 3A4 (CYP3A4): CYP3A is both the most abundant and most clinically significant member of the cytochrome P450 family of enzymes. The CYP3A family is actually composed of three major enzymes, CYP3A4 being the most commonly associated with drug interactions. The CYP3A isoenzyme subfamily makes up approximately 50% of the liver’s total cytochrome P450 and is also located in the small intestine and is ultimately responsible for the majority of first-pass metabolism. This is important as increases or decreases in first-pass metabolism can have the effect of administering a much smaller or larger dose than usual.

The most notable inducers of CYP3A4 include the glucocorticosteroids, rifampin (Rifadin; Rimactane), carbamazepine (e.g., Tegretol), phenobarbital, phenytoin (e.g., Dilantin), nevirapine (Viramune), and efavirenz (Sustiva). Compounds known to inhibit CYP3A4 include erythromycin, clarithromycin (Biaxin), ketoconazole, cyclosporine (e.g., Sandimmune), verapamil

(Calan), and grapefruit juice. With regard to the HIV protease inhibitors—all are substrates of CYP3A4—ritonavir is the most powerful CYP3A4 inhibitor, not only of all the protease inhibitors, but of most drugs in general. Indinavir (Crixivan), nelfinavir (Viracept), amprenavir (Agenerase), and lopinavir (Kaletra) appear to inhibit CYP3A4 equally, whereas saquinavir (Fortovase) is the least likely to inhibit this isoenzyme system. In the non-nucleoside reverse transcriptase inhibitor class, delavirdine is a potent, irreversible inhibitor of CYP3A4. In this way, delavirdine is the only non-nucleoside reverse transcriptase inhibitor (NNRTI) that has a profound effect on ritonavir serum concentrations.

Dr. Pau made it clear that there is definitely a handful of drugs that all health-care providers should worry about in relation to CYP3A4. Calcium channel blockers, for example, are avidly metabolized by CYP3A4 during the first pass. Other substrates to watch for include proarrhythmic agents that undergo extensive first-pass metabolism such as terfenadine (Seldane) and astemizole (Hismanal). HMG CoA reductase inhibitors (“statins”), which are frequently prescribed to manage lipid abnormalities associated with HAART, should also be used with caution (see Table 1). Simvastatin (Zocor) is generally contraindicated in patients receiving protease inhibitors. Atorvastatin (Lipitor) is a possi-

bility, though the starting dose should be reduced and then titrated, if necessary, to achieve the desired cholesterol-lowering effect. Conversely, standard doses of pravastatin (Pravachol) are generally considered safe for HIV-positive individuals being treated with a CYP3A4-inhibiting protease inhibitor or NNRTI, although a pravastatin dose increase might also be necessary if the desired effect is not achieved. "Regardless of which 'statin' is used," Dr. Pau cautioned, "it is important for health-care providers to monitor LFTs and CPK levels in their patients who are taking these drugs along with a protease inhibitor."

Cytochrome P450 2D6 (CYP2D6): CYP2D6 comprises a relatively small but significant percentage of the total cytochrome P450 in the liver. Only 2% to 6% of total liver cytochrome P450 is CYP2D6, but approximately one-fifth of clinically useful medications are metabolized by this enzyme. In particular, many antiarrhythmics and beta-blockers are metabolized by CYP2D6. In addition, CYP2D6 is responsible for the conversion of codeine to morphine, accounting for the majority of its analgesic effects. Unlike other CYP enzymes, there are no known inducers of this activity, except pregnancy. Several medications are known to inhibit CYP2D6, the most potent of which include quinidine, paroxetine (Paxil), and fluoxetine (Prozac). Other inhibitors include: sertraline (Zoloft), thioridazine (Mellaril), cimetidine (Tagamet), amiodarone (Cordarone), diphenhydramine, haloperidol (Haldol), and ticlopidine (Ticlid). Of the anti-HIV drugs, only ritonavir is known to inhibit CYP2D6 activity.

Cytochrome P450 2C9 (CYP2C9): CYP2C9 is responsible for the metabolism of several common medications, including many of the nonsteroidal anti-inflammatory drugs (NSAIDs) and phenytoin. While warfarin is also metabolized by CYP2C9, it is important to remember that this drug is administered as a mixture of two isomers [R(+) and S(-)] and is metabolized as two separate drugs. While (S)-warfarin is metabolized by CYP2C9, the (R)-warfarin isomer is metabolized in the liver by several isoenzymes, including CYP1A2 and CYP3A4. It is the (S)-warfarin that is responsible for most of the anticoagulation activity.

The rifamycins, as well as ritonavir, are consistent inducers of CYP2C9 activity. The barbiturates, carbamazepine, and

ethanol also appear to be significant, but less consistent, CYP2C9 inducers. Of the antiretroviral drugs, both ritonavir and nelfinavir have been shown to induce CYP2C9. Amiodarone (Cordarone), TMP/SMX, fluvastatin (Lescol), metronidazole (Flagyl), and fluconazole (Diflucan) are only a few of the many potent inhibitors of this enzyme activity. (*Editor's note: A detailed discussion of the drug-interaction problems between the protease inhibitors and the rifamycins can be found in an article published in the December 2001 issue of The PRN Notebook: "Double Scourge: Tuberculosis and HIV Coinfection." Guidelines pertaining to the coadministration of these two classes of drugs vary, depending on whether it is latent TB infection or active TB that is being treated, and are important to consider before prescribing any anti-tuberculosis agents.*)

Dangerous Liaisons: Interactions with MDMA and GHB

SOME DRUG INTERACTIONS CAN NEITHER BE foreseen nor prevented with a prescription pad. There will always be HIV-positive individuals—probably a large number of them—who take pharmacology into their own hands in the form of recreational drug use. In and of themselves, numerous recreational drugs are associated with a vast number of deleterious effects. When they are combined with certain prescribed medications, any of the life-endangering risks and caveats tied to illicit drugs can—and often do—increase significantly (see Table 2).

MDMA: At the top of Dr. Pau's list of potentially dangerous interactions is 3,4-methylenedioxy methamphetamine (MDMA)—ecstasy. This synthetic, psychoactive analogue of methamphetamine has both stimulant and hallucinogenic effects and is both readily accessible and immensely popular as a recreational drug. While intense exhilaration and euphoria are often the desired effects of the drug, agitation and panic are usually not far behind. High doses can lead to angina, cardiovascular collapse, convulsions, renal compromise, hepatic failure, and cerebral hemorrhage. Death is also possible with high levels, because of rupture or collapse of blood vessels in the brain, acute cardiac failure, or hyperthermia.

MDMA—like other amphetamines—is metabolized by way of the CYP2D6 isoenzyme. While this renders ecstasy and other forms of methamphetamine (e.g., "crystal meth") free of any immediate interactions with most of the protease inhibitors and NNRTIs, trouble remains a possibility with ritonavir, an inhibitor of this P450 enzyme.

At least one death, believed to be the result of a ritonavir/MDMA mix, has been reported thus far. The case discussed by Dr. Pau involved a 32-year-old HIV-positive British male with a history of alcohol-related liver disease, who died of an MDMA overdose on October 6, 1996. He had been taking a standard dose of ritonavir (600 mg BID) for approximately two weeks. On the night of his death, he had taken two and a half MDMA tablets (150 mg in total) and had consumed four beers. Soon after taking the extra half tablet, he became hypertensive; his respiratory rate peaked at 45 and his heart rate exceeded 140 bpm. He then became cyanotic, experienced a tonic-clonic seizure and vomiting, went into cardiac arrest, and died later that night.

The concentration of MDMA in his blood was 3.56 mg/L—the equivalent of taking 22 ecstasy tablets. Following additional toxicological investigations, it was concluded that inhibition of CYP2D6 by ritonavir and alcohol ingestion contributed to the high MDMA levels and his unfortunate death. However, some experts note that there is no way to say with certainty if this was truly a drug-drug interaction; other possibilities include abnormal CYP2D6 function or self-administration of a large MDMA dose. What's more, there have been no studies that have examined the extent of the interaction between MDMA and ritonavir (John Gerber, personal communication).

GHB: Dr. Pau also discussed a case report published in 1999 by Robert Harrington, MD, and his colleagues at the University of Washington School of Medicine and School of Pharmacy in Seattle (Harrington, 1999). The report described an HIV-positive man receiving treatment with ritonavir and saquinavir who experienced a prolonged stimulatory effect from a small dose of MDMA and a near-fatal reaction from a small dose of [gamma]-hydroxybutyrate (GHB).

The 29-year-old man became unresponsive within 20 minutes after ingesting approximately half a teaspoon of GHB. Emergency personnel noted shallow respirations and a heart rate of 40 bpm. They

