


Drug Interactions and Anti-HIV Therapy

Liz
Highleyman



The advent of highly active antiretroviral therapy (HAART) has decreased mortality and improved the quality of life for HIV positive people, but treatment of HIV and its associated conditions remains highly complex. With some 20 antiretroviral agents, dozens of drugs for opportunistic illnesses (OIs), and additional therapies to manage associated conditions such as elevated blood fats, the potential for drug interactions is a pressing concern.

Interactions happen when one drug influences the level or activity of another. Because of the way they are processed in the body, protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are especially likely to be involved. Interactions may raise blood levels of a drug, possibly causing intensified side effects, or they may decrease drug concentrations, potentially resulting in reduced effectiveness. But drug interactions are not always problematic: the PI ritonavir (Norvir) can “boost” levels of other drugs in its class, increasing their potency and allowing for more convenient dosing.

With so many drugs to consider, it is not possible to give a comprehensive listing of every possible interaction. Instead, this article will discuss how and why drug interactions occur, describe some of the important interactions commonly seen with antiretroviral therapy, and offer steps to avoid or manage them. The accompanying resource list on page 28 provides useful online drug interaction databases and tools to help determine whether specific medications are likely to interact.

HIV positive people should be aware of the potential for interactions and inform all their health-care providers about all drugs they are taking, including prescription and over-the-counter (OTC) medications, herbal remedies and supplements, and recreational or street drugs.

A Ubiquitous and Growing Problem

The antiepileptic drug phenytoin (Dilantin) can dangerously decrease levels of lopinavir/ritonavir (Kaletra). Use of the antibiotic erythromycin with PIs may increase the risk of sudden cardiac death. The new PI atazanavir (Reyataz) should not be used with omeprazole (Prilosec), a popular medication for gastroesophageal reflux. Boosted saquinavir (Invirase) can potentially cause liver toxicity when combined with rifampin, part of the standard first-line regimen for tuberculosis.

These are just a few of the interactions between anti-HIV medications and other drugs that have been announced in “Dear Doctor” advisories or described in medical journals during the past year. As novel agents are approved and additional information about existing products becomes available, new interactions continually come to light. Uncovering potential interactions is a major focus of the drug development process and—as shown by the amount of time and space devoted to the topic at professional conferences and in the medical literature—avoiding and managing drug interactions has become an increasingly important part of HIV medicine.

Today most HIV positive people receiving treatment take antiretroviral regimens consisting of three or more drugs from at least two different classes. Many also use various medications, such as antifungals and cholesterol-lowering statins, to treat associated conditions and manage side effects. OTC medications, street drugs, methadone, alternative and complementary therapies, and even certain foods may also be involved in interactions.

This exploding “polypharmacy” presents a challenge for people with HIV and their providers. While many drug interactions are of little clinical significance, others can lead to severe toxicities, loss of virological control of

HIV, and the emergence of drug-resistant virus. Fortunately, a relatively small subset of drugs is implicated in the lion’s share of interactions; often problems can be avoided by heightened vigilance and judicious substitution of effective alternatives.

Mechanisms of Drug Interactions

Drug interactions fall into two broad categories: pharmacodynamic and pharmacokinetic.

Pharmacodynamic interactions are those related to the combined clinical activity of two or more agents used together, for example, additive or synergistic side effects (see below). Pharmacokinetic interactions occur when one agent changes the blood concentration of another. The majority of clinically significant drug interactions encountered in HIV medicine are pharmacokinetic in nature.

Pharmacodynamic Effects

Some drug interactions occur when similar agents, or agents with similar effects, are used together. An additive effect refers to the combined effects of two or more agents added together (i.e., $1 + 1 = 2$). A synergistic effect occurs when the overall effect of two or more agents used together is greater than the sum of the effects the compounds would produce if used separately (i.e., $1 + 1 = 3$). An antagonistic effect happens when one agent reduces or cancels out the effects of another (i.e., $1 + 1 = 0$).

Successful HAART relies on additive effects. Not long after the advent of the first antiretroviral drugs, it became clear that single agents used alone (monotherapy) could not suppress HIV

over the long term since the virus can mutate to develop drug resistance. Therefore, multiple agents from more than one drug class are now used to construct effective regimens.

Additive and synergistic side effects are a major concern in anti-HIV therapy. When two or more drugs with overlapping toxicity profiles are used together, the combined toxicity may prove intolerable, even if the individual agents alone produce only mild side effects. For instance, the “d drugs”—ddC (zalcitabine, Hivid), ddI (didanosine, Videx), and d4T (stavudine, Zerit)—can all cause pancreatitis (inflammation of the pancreas), peripheral neuropathy (nerve damage), and mitochondrial toxicity. Thus, experts recommend that combinations of these drugs should be avoided if possible.

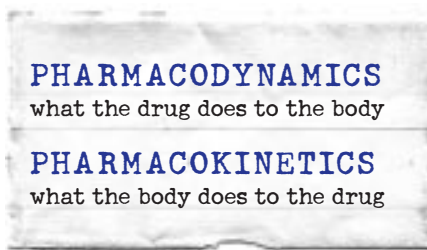
An Introduction to Pharmacokinetics

Pharmacokinetics refers to what happens to drugs in the body: their absorption, metabolism (processing), transport, distribution to tissues, and elimination.

In a nutshell, the plasma concentration of a drug varies between doses. The goal is to achieve a minimum, or trough, concentration (C_{\min}) that is effective without causing unacceptable toxicity at the highest, or peak, level (C_{\max}). The total exposure to a drug between one dose and the next is called the area under the curve, or AUC. If a drug has a narrow therapeutic range—meaning a small difference between an effective dose and a toxic one—even minor interactions may prove problematic.

Altered Absorption and Transport

Most medications are taken orally and absorbed from the stomach and intestines. Any agent that changes the gastrointestinal environment can affect drug absorption, which is why some medications have food restrictions. Many agents are better absorbed when the stomach is empty, but

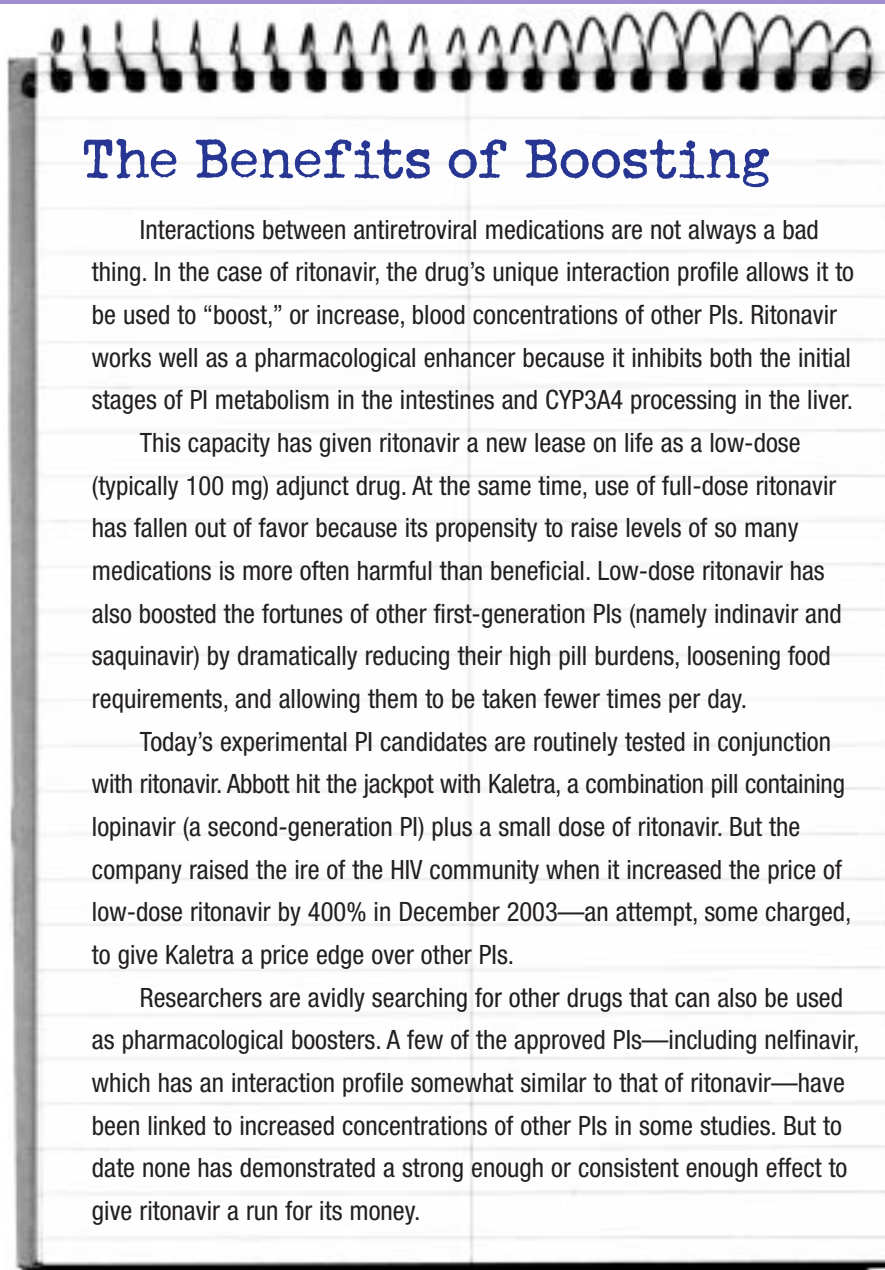


some—including nelfinavir (Viracept)—are better absorbed when taken with food. Lipid-soluble (dissolvable in fat) compounds require fatty foods for optimal absorption; however, one such agent, efavirenz (Sustiva), should be taken without fat in order to slow absorption and reduce side effects.

Medications that neutralize the acidity of gastric secretions (that is, increase their pH) can interfere with the absorption of other drugs, such as atazanavir, that require an acid environment. The old formulation of ddI contained an antacid buffering agent and thus could not be taken at the same time as several other drugs; this is not a concern with the newer, long-acting enteric-coated form of ddI (Videx EC). For the same reason, certain drugs should not be taken with acid-lowering medications. In addition, some agents can combine with one another in the stomach (a process called chelation), resulting in insoluble compounds that cannot be absorbed; this can occur when some drugs are taken with certain minerals.

The initial phase of drug absorption and metabolism occurs in the intestines. Cells in the intestinal lining contain transporter proteins, called P-glycoproteins, that act as “pumps” to return drug molecules back into the intestine for excretion rather than allowing them to enter the bloodstream. P-glycoproteins also pump certain drugs out of individual cells throughout the body and are associated with drug resistance. Agents that promote P-glycoprotein activity (including some antiretroviral drugs) cause lower plasma drug concentrations, while P-glycoprotein inhibitors increase drug levels.

Once successfully absorbed, the drug enters the bloodstream. Agents are carried in the plasma in either a free (unbound) form or bound to blood proteins such as albumin; the bound form is not bioavailable and cannot enter tissues. Thus, agents that alter protein binding can affect



The Benefits of Boosting

Interactions between antiretroviral medications are not always a bad thing. In the case of ritonavir, the drug's unique interaction profile allows it to be used to “boost,” or increase, blood concentrations of other PIs. Ritonavir works well as a pharmacological enhancer because it inhibits both the initial stages of PI metabolism in the intestines and CYP3A4 processing in the liver.

This capacity has given ritonavir a new lease on life as a low-dose (typically 100 mg) adjunct drug. At the same time, use of full-dose ritonavir has fallen out of favor because its propensity to raise levels of so many medications is more often harmful than beneficial. Low-dose ritonavir has also boosted the fortunes of other first-generation PIs (namely indinavir and saquinavir) by dramatically reducing their high pill burdens, loosening food requirements, and allowing them to be taken fewer times per day.

Today's experimental PI candidates are routinely tested in conjunction with ritonavir. Abbott hit the jackpot with Kaletra, a combination pill containing lopinavir (a second-generation PI) plus a small dose of ritonavir. But the company raised the ire of the HIV community when it increased the price of low-dose ritonavir by 400% in December 2003—an attempt, some charged, to give Kaletra a price edge over other PIs.

Researchers are avidly searching for other drugs that can also be used as pharmacological boosters. A few of the approved PIs—including nelfinavir, which has an interaction profile somewhat similar to that of ritonavir—have been linked to increased concentrations of other PIs in some studies. But to date none has demonstrated a strong enough or consistent enough effect to give ritonavir a run for its money.

how much active drug reaches a site of action.

The CYP450 System

Drugs are metabolized, or bio-transformed, into byproducts that can more easily be excreted in the feces or urine. Before it is circulated throughout the body, blood leaving the gastrointestinal tract first passes through the liver, where most drug processing occurs. One type of hepatic drug metabolism is carried out by a group of enzymes (proteins that facilitate

chemical reactions) known as the cytochrome P450 (CYP450) system. In addition to the liver, CYP450 enzymes are also present in the intestines and elsewhere in the body.

There are some two dozen CYP450 isoenzymes (specific variants), classified into families designated by numbers and letters, but a small subset carries out most drug metabolism. Many agents are metabolized by a single isoenzyme, but others are processed by more than one. The most abundant isoenzyme, CYP3A4,

is responsible for metabolizing about half of the drugs currently on the market.

Drug metabolism is limited by the quantity of CYP450 enzymes, and different agents compete for their use. Some drugs, called CYP450 inhibitors, retard the activity of these enzymes (ritonavir and erythromycin are examples of inhibitors). When an inhibitor of a specific isoenzyme is present, the processing of other drugs that require the same enzyme is slowed, causing blood concentrations of these other drugs to increase. (This is why ritonavir can be used to boost levels of other PIs; see sidebar on page 22.) Other agents, called CYP450 inducers, cause cells to produce more of a specific isoenzyme over time (rifampin and phenytoin are examples of inducers). When such an agent is present, drugs that are metabolized by the now more abundant isoenzyme are processed more rapidly, causing their blood concentration to fall.

After they are processed and distributed to tissues, drugs must be eliminated. Some drug metabolites are excreted in bile and eliminated through the feces, while others are processed by the kidneys and eliminated in the urine. Any factors that impair or inhibit the filtering activity (tubular secretion) of the kidneys can slow the processing of drugs that rely on this mechanism, again allowing them to reach higher plasma concentrations. For this reason, people with renal insufficiency (kidney dysfunction) are more prone to drug interactions and side effects.

As described by Stephen Piscitelli, PharmD, and Keith Gallicano, PhD, in an overview of antiretroviral and OI drug interactions in the March 29, 2001 issue of the *New England Journal of Medicine (NEJM)*, pharmacokinetic interactions among drugs used in HIV therapy are often “multifactorial,” involving altered drug absorption, P-glycoprotein modulation, CYP450 induction and/or inhibition, changes in renal elimination, and fluctuations in intracellular drug concentration.

Factors that Impact Drug Interactions

Drug interactions are not the same in all people. Several factors can influence pharmacokinetics, including sex, age, race/ethnicity, pregnancy, hormone levels, body size, alcohol use, and coexisting conditions such as liver or kidney dysfunction. For instance, individuals may possess genetic variations, or polymorphisms, that affect expression of specific CYP450 enzymes. A study presented at the February 2004 Retrovirus conference, for example, revealed that people of African descent are seven times more likely than white people to carry a specific variant of the gene controlling expression of the CYP2B6 isoenzyme; as a result, black people as a group eliminate efavirenz more slowly, potentially leading to more intense side effects but also greater efficacy. P-glycoprotein expression also varies by racial/ethnic group.

The impact of liver disease is of particular concern since a substantial proportion of HIV positive people have chronic hepatitis B or C coinfection, which can lead to liver damage including fibrosis and cirrhosis (scarring). When the liver is damaged—as a result of viral hepatitis, heavy alcohol use, drug toxicity, or some other cause—its ability to process drugs may be impaired, potentially leading to higher blood concentrations.

As reviewed by David Wyles, MD, and John Gerber, MD, in the January 1, 2005 issue of *Clinical Infectious Diseases (CID)*, several studies have shown that the pharmacokinetics of antiretroviral drugs may be significantly altered in HIV positive people with hepatitis B or C, and that such impairment is more pronounced in those with more advanced liver damage. For example, L. Becquemont and colleagues demonstrated that CYP3A4 and CYP2D6 isoenzyme activity decreased by 65% and 81%, respectively, in HCV-infected subjects compared with uninfected individuals. At the functional level, other research

has demonstrated impaired drug clearance in people with liver damage.

Wyles and Gerber concluded that liver dysfunction has a considerable impact on PI metabolism, but on the whole, NNRTI and nucleoside reverse transcriptase inhibitor (NRTI) processing are minimally affected. Fortunately, altered drug metabolism in people with liver damage can often be managed by adjusting drug doses. The authors cautioned, however, that making generalized recommendations for dose reduction is difficult, “given the highly variable pharmacokinetics of PIs across the population.”

Interactions Involving Antiretrovirals

Several antiretroviral drugs are both CYP450 and P-glycoprotein substrates (targets). It is therefore not uncommon to encounter interactions among them or with agents used to treat other conditions. Drug interactions involving the NRTI, NNRTI, and PI classes are discussed below. The remaining approved anti-HIV drug, the entry inhibitor T-20 (enfuvirtide, Fuzeon), must be taken by injection because it would be destroyed by acid in the stomach. As reported by Indravadan Patel and colleagues from Roche in the February 2005 issue of *Clinical Pharmacokinetics*, T-20 has no known interactions with other antiretroviral medications.

NRTIs

NRTIs are prone to pharmacodynamic interactions such as additive and synergistic toxicities, but because they are primarily eliminated by the kidneys, not the liver, they have little impact on the CYP450 system. As such, NRTIs have few known pharmacokinetic interactions with NNRTIs or PIs. AZT (zidovudine, Retrovir) is processed by glucuronyl transferases in the liver, and agents that affect levels of these enzymes can raise or lower AZT blood levels. Abacavir (Ziagen), alone among the NRTIs, is broken down by the same enzyme that metabolizes alcohol; thus,

concurrent use of alcohol may raise abacavir levels.

Tenofovir DF (Viread), the only approved nucleotide reverse transcriptase inhibitor, has some unique interactions. Tenofovir can increase plasma levels of both buffered and enteric-coated ddI dramatically (by more than 50% in some studies). In one case, a man with pre-existing kidney dysfunction died of kidney failure and lactic acidosis (a known side effect of ddI) after taking the two drugs together. When using this combination, the ddI dose should be reduced and individuals should be monitored for ddI-related toxicities. Tenofovir can decrease blood concentrations of atazanavir, so levels of this PI should be increased through higher dosing or boosting with ritonavir. Conversely, atazanavir—as well as lopinavir—increases tenofovir levels, but dose adjustment is generally not necessary; tenofovir does not appear to interact with saquinavir, nelfinavir, or indinavir (Crixivan).

NNRTIs

All three approved NNRTIs impact the CYP450 system: nevirapine (Viramune) is a CYP3A4 inducer, delavirdine (Rescriptor) is a CYP3A4 inhibitor, and efavirenz combines both effects. The NNRTIs also induce and/or inhibit other isoenzymes that play more minor roles in drug interactions.

Nevirapine and efavirenz speed processing and reduce plasma concentrations of other drugs metabolized by CYP3A4. In particular, these NNRTIs can cause levels of some PIs to fall, necessitating higher doses and/or boosting with ritonavir. They also lower concentrations of a variety of other agents metabolized by the CYP450 system, including methadone and oral contraceptives, potentially resulting in decreased efficacy.

Efavirenz and delavirdine (which is no longer recommended for first-line therapy) can increase levels of some PIs and other types of medication metabolized by the liver. Caution

is advised when combining these NNRTIs with drug classes that can reach potentially dangerous concentrations when used with CYP450 inhibitors.

Given its mixed inducer/inhibitor effect, as well as its purported influence on other isoenzymes besides CYP3A4, efavirenz can increase nelfinavir and ritonavir levels even though it decreases concentrations of atazanavir, lopinavir, indinavir, saquinavir, and fosamprenavir (Lexiva). Efavirenz has been shown to lower atazanavir concentrations by about 75%; while its effect on other PIs is less dramatic, it should not be used with unboosted indinavir or saquinavir.

Caution is warranted when combining NNRTIs with CYP450 inducers such as rifampin, since these can lower NNRTI levels. It is also important to remember that NNRTIs have long half-lives, meaning they stay in the body for an extended period after discontinuation; this should be taken into account when stopping an NNRTI and substituting a potentially interacting drug. A final caveat with nevirapine is to avoid or use with caution other drugs that may cause skin rash or liver toxicity, due to the potential for overlapping side effects.

PIs

As a class, the PI drugs raise the most concern related to drug interactions. All approved PIs are metabolized by the CYP3A4 isoenzyme and are CYP3A4 inhibitors, but some are stronger than others and some have additional effects. A retrospective chart review conducted soon after the advent of first-generation PIs (published in the March 1997 issue of *Clinical Pharmacokinetics*) revealed that the probability of experiencing undesirable drug interactions was 31% after starting indinavir, 42% after starting saquinavir, and 77% after starting ritonavir. For subjects with CD4 cell counts below 100 cells/mm³ the risk was even greater: 55%, 63, and 93%, respectively.

Saquinavir has the mildest CYP3A4 inhibitory effect, and is therefore the least likely to affect levels of other drugs. Atazanavir, fosamprenavir, indinavir, and nelfinavir are all moderate inhibitors. In contrast, ritonavir is so potent in this respect that it can be used to boost blood concentrations of other drugs in its class (see “The Benefits of Boosting” on page 22). Unlike other approved PIs, ritonavir and nelfinavir both also induce CYP3A4, and share the interesting property of being able to induce their own metabolism. Little is known about the use of lopinavir alone, since it is coformulated with ritonavir in the Kaletra combination pill.

Like all CYP450 inhibitors, PIs slow the processing of other medications metabolized by the same isoenzymes, potentially allowing them to reach highly toxic concentrations. Full-dose ritonavir presents the greatest risk; the smaller ritonavir dose in the Kaletra pill (100 mg) or used to boost other PIs is less likely to cause problematic interactions. Some of the drugs that warrant extra caution or should be avoided altogether when used with PIs include certain statins, anticonvulsants, benzodiazepines, and calcium-channel blockers. (Problematic drug classes are discussed in more detail below.)

Because PI interaction profiles vary in some important respects, each new drug in this class must be extensively tested to determine how it will behave under “real world” conditions. For example, as reported in the January 28, 2005 issue of *AIDS*, a recent clinical trial (ACTG 5143) revealed that combining fosamprenavir plus lopinavir led to significantly reduced levels of both amprenavir (the active metabolite of fosamprenavir) and lopinavir; as a result, enrollment in the study was halted. Unlike most of its classmates, tipranavir (Aptivus), a nonpeptidic PI recently granted approval, is a CYP3A4 inducer. In a study by Sharon Walmsley, MD, and

colleagues presented at the XV International AIDS Conference in Bangkok in July 2004, tipranavir reduced minimum plasma concentrations of amprenavir (Agenerase), lopinavir, and saquinavir by 51%, 45%, and 84%, respectively. As such, tipranavir should be avoided or used cautiously in conjunction with other PIs.

Even as PIs impact levels of other drugs metabolized by the CYP450 system, they themselves are subject to alteration by CYP450 inducers and inhibitors. Inducers present the most concern since they can potentially lead to subtherapeutic PI levels, viral breakthrough (increase in viral load), and the development of drug-resistant HIV.

Interactions with Other Types of Drugs

While a complete list of known and theoretical interactions between antiretrovirals and other types of drugs is beyond the scope of this article, a few categories of medications warrant particular attention because they are commonly used by people with HIV or because their interactions are particularly frequent and/or clinically significant.

For the most part, the drugs discussed below are CYP450 substrates. To refresh, agents that inhibit CYP450 enzymes tend to increase concentrations of other drugs, while agents that induce CYP450 enzymes usually decrease drug concentrations. In actual practice, most of the following medications are of concern either because they reduce antiretrovirals to subtherapeutic levels, or because anti-HIV drugs raise them to dangerously toxic levels. However, for almost every general rule about interactions between drug classes, there are exceptions and special cases.

HIV positive individuals should educate themselves about common drug interactions and health-care professionals should keep up to date with the medical literature in this field, and especially with advisories

issued by the Food and Drug Administration (FDA) or pharmaceutical companies regarding newly discovered interactions. Monitoring for effectiveness and toxicity should be performed regularly, especially when adding or changing medications.

Drugs Used to Treat OIs

Several antifungal and antibiotic drugs used to treat OIs are prone to interactions with some PIs and NNRTIs. The "azole" antifungals are CYP3A4 and P-glycoprotein inhibitors, some of which can increase concentrations of other medications metabolized by these pathways. Conversely, CYP3A4 inhibitors can raise azole levels. Use of voriconazole (VFEND) with ritonavir (400 mg dose) or efavirenz is contraindicated. Fluconazole (Diflucan) is associated with fewer interactions than itraconazole (Sporanox) or ketoconazole (Nizoral).

Macrolide antibiotics, including erythromycin and clarithromycin (Biaxin), also inhibit both CYP3A4 and P-glycoprotein. As reported in the September 9, 2004 issue of *NEJM* (and summarized in the last issue of *BETA*), erythromycin appears to increase the risk of fatal cardiac arrhythmias (heart rhythm disturbances) when coadministered with drugs metabolized by CYP3A4. Although the authors of this study did not look at PIs specifically, they found that subjects using erythromycin along with other CYP3A4 inhibitors had a risk of sudden cardiac death five times higher than that seen in individuals not taking such a combination. A related macrolide, azithromycin (Zithromax), has a minimal effect on CYP450 enzymes and may be a suitable alternative to erythromycin or clarithromycin.

Interactions between antiretrovirals and drugs used to treat tuberculosis (TB) are a growing concern, especially in resource-limited countries where TB remains a major cause of AIDS-related death. Rifampin (known as rifampicin outside the U.S.), part of

standard first-line regimens for TB prophylaxis and treatment, is one of the most potent CYP3A4 inducers known, and can reduce PIs to subtherapeutic levels. The optimal regimen for treating active TB in people with HIV remains unclear; physicians must weigh the superior efficacy of rifampin against concerns about interactions with antiretroviral drugs.

The azoles, macrolides, and rifamycins can interact not only with antiretrovirals, but also with each other. On account of this complexity, the care of HIV positive people who require treatment for multiple OIs should be managed by experienced physicians.

Acid-Lowering Drugs

As noted previously, medications that neutralize the acidity of gastric secretions can interfere with the absorption of drugs like atazanavir that require an acid environment. Such medications are often taken to relieve gastroesophageal reflux, or "heartburn." OTC antacids (e.g., TUMS, Maalox) and buffered medications typically exert their acid-neutralizing effects for only a short time, making it possible to use them within 1–2 hours of acid-dependent drugs.

Other types of acid-lowering agents are much longer-acting. Proton pump inhibitors (e.g., omeprazole [Prilosec], esomeprazole [Nexium], lansoprazole [Prevacid]), which block the production of stomach acid, can alter gastric pH for 24 hours or longer. In December 2004 Bristol-Myers Squibb warned against the use of ritonavir-boosted atazanavir plus omeprazole after a study revealed a 76% reduction in atazanavir plasma concentrations when the drugs were coadministered. (The study used the 40 mg prescription dose of omeprazole; it is not known whether the 20 mg OTC dose would have a similar effect.) Data are forthcoming on the safety of atazanavir plus histamine-2 (H2) receptor antagonists, another class of acid-lowering agents that includes cimetidine (Tagamet) and ranitidine (Zantac).

For further reading

Package inserts for approved drugs—included with purchased medications or available from a pharmacist or on the internet. Check pharmaceutical company web sites; most have sites for specific drugs, often with URLs that include the drugs' brand names (e.g., www.reyataz.com)

HIV Drug-Drug Interactions—The Body's listing of the latest drug interaction news, research, tools, and specific medication alerts (www.thebody.com/treat/interactions.html)

Polypharmacy Problems: Drug Interactions in the Multidrug Therapy of HIV Infection—article by Alice Pau, PharmD, and Tim Horn. *PRN Notebook*, March 2002; includes interaction charts featuring lipid-lowering agents, herbal/nutraceutical therapies, and illicit/recreational drugs (www.prn.org/prn_nb_cntnt/vol7/num1/pau_frm.htm)

What's PK Got to Do with It?—the Winter 2005 issue of *Positively Aware* features a series of articles on pharmacokinetic basics and how the three major antiretroviral drug classes work and interact (www.tpan.com/publications/positively_aware/winter_05_pk/pk_34_web.pdf)

Clinically Significant Drug Interactions Associated with Highly Active Antiretroviral Therapy—article by John Faragon, PharmD, and Peter Piliero, MD. HIV Education Prison Project, January 2004 (www.idcronline.org/archives/jan04/mainarticle.html); accompanying chart, Drug Interactions with HAART and Methadone (www.idcronline.com/archives/jan04/hiv101.pdf)

Drug Interactions: HIV Medications, Street Drugs and Methadone—article by James Learned and Maia Szalavitz. *ACRIA Update*, Spring 2005 (www.thebody.com/cria/spring05/interactions.html)

Cholesterol-Lowering Medications

As HAART extends the lives of people with HIV, elevated blood lipids (fats) associated with PIs are a growing concern because high cholesterol and triglyceride levels are linked to increased cardiovascular disease risk. As such, many people taking PI-based antiretroviral regimens are also using medications to lower their lipids.

One class of commonly used cholesterol-lowering agents, the "statins," are metabolized by the CYP450 system

and their concentrations can be increased by PIs (particularly ritonavir). But not all statins are equal. In November 2000 the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group recommended that people on HAART should start with low doses of pravastatin (Pravachol), atorvastatin (Lipitor), or fluvastatin (Lescol), which appear to interact least with antiretrovirals. The panel advised against use of lovastatin (Mevacor) or simvastatin (Zocor), which can reach dangerously

high levels when used with PIs, potentially leading to intensified side effects including rhabdomyolysis (muscle damage) and kidney failure. The interaction profile of the newest statin, rosuvastatin (Crestor), has not yet been well defined.

Medications for Psychiatric Conditions

Certain anticonvulsant or anti-epilepsy drugs—notably phenytoin (Dilantin), carbamazepine (Tegretol), and phenobarbital (Solfoton)—are potent CYP450 inducers that can potentially render some PIs and NNRTIs ineffective. Certain PIs, including lopinavir, can also decrease phenytoin levels. More suitable alternatives for use with HAART include divalproex sodium (Depakote), gabapentin (Neurontin), lamotrigine (Lamictal), and levetiracetam (Keppra). Monitoring of antiseizure drug levels in the blood may help avoid excessive or suboptimal dosing.

Among the benzodiazepines, a class of sedatives used to treat anxiety and insomnia, midazolam (Versed) and triazolam (Halcion) may reach dangerously high concentrations when used with CYP450 inhibitors, potentially causing fatal respiratory depression. Caution is also warranted concerning alprazolam (Xanax), diazepam (Valium), and zolpidem (Ambien). Safer alternatives include lorazepam (Ativan) and temazepam (Restoril).

Among medications used to treat depression, drugs in the tricyclic antidepressant class are most likely to be involved in CYP450-mediated interactions. Levels of the more commonly used selective serotonin reuptake inhibitors (SSRIs)—including fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), and escitalopram (Lexapro)—may also be increased by CYP450 inhibitors; excessive SSRI levels can cause symptoms such as seizures, heart rhythm abnormalities, and coma. When taken with PIs, especially ritonavir, antidepressant doses may need to be reduced. Here again,

drug level monitoring may help avoid interaction problems.

Many people with HIV see separate providers for HIV-related and mental health care. Due to the potential for antiretroviral and psychiatric drug interactions, it is important that all providers know about all the drugs their patients are using and work together to determine appropriate regimens.

Oral Contraceptives

Agents that impact CYP3A4 can significantly reduce plasma concentrations of estrogen and other steroid hormones. In women using oral contraceptives containing ethinyl estradiol or other forms of estrogen, concurrent use of efavirenz, nevirapine, nelfinavir, ritonavir, or lopinavir may decrease hormone levels enough to cause unintentional pregnancy. HIV positive women taking these antiretrovirals should use a backup contraception method along with combination estrogen/progesterone pills, birth control pills that contain only progesterone, or a barrier method (e.g., condoms).

Erectile Dysfunction Drugs

Levels of the erectile dysfunction drugs sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis) may rise when used with PIs. For example, studies have shown that sildenafil concentrations increased by more than four-fold when coadministered with ritonavir. Excessive plasma levels of these drugs may cause low blood pressure, dizziness, fainting, headaches, vision disturbances, and/or priapism (painful, prolonged erections). Men using antiretrovirals that inhibit CYP3A4 should talk to their physicians about taking erectile dysfunction agents in lower doses and/or less often.

Other Medication Classes

PIs can increase plasma levels of ergot alkaloid derivatives (e.g., Cafegot, Migranal) used to treat migraine headaches; coadministration of these drugs should be avoided.

Levels of calcium-channel blockers (e.g., diltiazem, verapamil), used to treat conditions such as angina (chest pain), high blood pressure, and cardiac arrhythmias, may also increase in the presence of CYP3A4 inhibitors.

PIs can also interact dangerously with immunosuppressive drugs (e.g., tacrolimus [Prograf]) used to prevent organ rejection after a transplant. One HIV positive liver transplant recipient at the University of Pittsburgh died from an organ rejection reaction several years ago when his hometown doctor took him off HAART, thereby causing his tacrolimus level to drop precipitously. This case illustrates the importance of physicians working together to determine appropriate medication combinations.

Recreational and Street Drugs

There have been few formal studies of interactions between antiretrovirals and recreational or street drugs, but anecdotal reports and pharmacokinetic data indicate that some such combinations may be harmful. In addition, street drugs may be cut with substances other than the advertised ingredient, which can also impact interactions.

Evidence suggests that ritonavir can increase blood concentrations of ecstasy (MDMA, "X"), which is metabolized by the CYP2D6 isoenzyme. Elevated ecstasy levels may

cause heightened agitation, seizures, increased heart rate, and/or cardiac arrest. The October 1996 death of a London man with pre-existing liver disease was widely attributed to concurrent use of ritonavir (which he had recently started) and a moderate dose of ecstasy (reportedly 2.5 tablets). Other forms of amphetamine, including crystal methamphetamine ("speed," "crank," "Tina"), share the same processing pathway and may have comparable interaction profiles. However, cocaine, also a stimulant, has not been reported to interact with antiretroviral medications.

Another worrisome party drug is gamma-hydroxybutyrate, or GHB. The combination of ritonavir, saquinavir, and modest doses of GHB and ecstasy may have been responsible for the nearly fatal respiratory arrest of a Seattle man reported in 1999. While there are minimal human data available, animal studies suggest that GHB is metabolized by the CYP450 system.

In both the London and Seattle cases, the individuals were found to have unusually high blood levels of their respective recreational drugs, but this may have been due to other factors (e.g., adulterated drugs, genetic variations in drug-processing enzymes) and cannot be definitively attributed to interactions with anti-HIV drugs.

Finally, ritonavir, other PIs, efavirenz, and nevirapine appear to

Antiretroviral drugs may interact with:*

Other anti-HIV medications	Benzodiazepines (e.g., alprazolam, midazolam, triazolam)
OI drugs (e.g., voriconazole, clarithromycin)	Oral contraceptives containing estrogen
Antituberculosis drugs (rifampin, rifabutin)	Erectile dysfunction drugs (e.g., sildenafil, vardenafil)
Antacids (e.g., omeprazole, cimetidine)	Recreational, street, or party drugs
Cholesterol-lowering statins (e.g., lovastatin, simvastatin)	Methadone
Antidepressant drugs (e.g., fluoxetine, sertraline)	Herbal remedies (e.g., St. John's wort, garlic)
Anticonvulsant drugs (e.g., phenytoin, phenobarbital)	

* not a comprehensive listing

Drug Interaction Resources

Online tools and databases:

University of Liverpool—comprehensive and frequently updated online database of antiretroviral drug interactions; includes charts in PDF format and an interactive database access tool (www.hiv-druginteractions.org)

HIV InSite—interactive tool allows searches by antiretroviral drug, interacting drug, and interacting drug class (www.hivinsite.com/arvdb?page=ar-00-02); the site also includes ARV Alert, featuring the latest safety alerts about antiretroviral drug interactions and adverse events (www.hivinsite.com/InSite?page=ar-alert)

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents—Table 19: Drugs That Should Not Be Used With PI or NNRTI Antiretrovirals; Table 20: Drug Interactions Between Antiretrovirals and Other Drugs (www.aidsinfo.nih.gov/guidelines/adult/AA_040705.pdf)

AIDSmads.com—simple tool for checking antiretroviral drug interactions (www.aidsmeds.com/cmm/DrugsNewContent.asp)

Project Inform—comprehensive list of interactions by drug; also includes a glossary and information about street drug interactions (www.projectinform.org/fs/drugin.html)

Party Smarty Marty—resource on interactions between anti-HIV medications and recreational drugs sponsored by the San Francisco Community Clinic Consortium and the Haight-Ashbury Free Clinic (www.hafreeclinics.org/drugs)

Drug Digest—includes drugs for all conditions and herbs by both common and Latin names; includes food and alcohol as well as drug-drug interactions (www.drugdigest.org/DD/Interaction/ChooseDrugs/1,4109,,00.html)

Medscape HIV/AIDS Clinical Calculator—checks interactions among drugs in a regimen and suggests appropriate dosing schedules (www.medscape.com/px/hivscheduler)

reduce plasma concentrations of opiates (e.g., heroin, numerous prescription pain-relievers), which could potentially reduce the risk of overdose, but may lead to withdrawal symptoms or inadequate pain relief.

Methadone

As is true with other opiates, some anti-HIV medications can raise or lower methadone plasma concentrations. In particular, the NNRTIs efavirenz and nevirapine, both CYP3A4 inducers, may decrease methadone levels enough to cause

withdrawal symptoms (e.g., runny nose, tearing eyes, excessive perspiration, nausea, abdominal cramps, convulsions) in people receiving methadone maintenance therapy. Studies—including one by Elinore McCance-Katz, MD, reported in the August 15, 2003 issue of *CID*—indicate that lopinavir can also decrease methadone levels, even though ritonavir alone might be expected to have the opposite effect. Taking fosamprenavir (or the older version, amprenavir) with methadone can lower levels of both drugs.

Physicians and methadone maintenance program staff should be aware of this potential effect, which may take as long as two weeks to fully emerge, and be prepared to monitor methadone levels and gradually increase methadone doses enough to avoid opiate withdrawal (perhaps by 25% or so).

Herbal Remedies

There has been little formal research on interactions between antiretroviral agents and herbal therapies, but in a few instances enough data have emerged to make recommendations. St. John's wort (*Hypericum perforatum*), used to relieve depression, induces both CYP3A4 and P-glycoproteins, and was associated with significantly decreased indinavir concentrations in one study. The U.S. government's antiretroviral treatment guidelines state that St. John's wort should not be used with PIs or NNRTIs; in February 2000 the FDA issued a public health advisory with the same message.

Garlic (*Allium sativum*) inhibits CYP3A4 activity, and high-dose garlic supplements reduced saquinavir levels in one study; however, the smaller amount of garlic normally consumed in food is unlikely to cause problems. Another herbal remedy that could interact pharmacokinetically with anti-HIV medications is milk thistle (and its derivative, silymarin), used to treat liver conditions including chronic hepatitis B and C.

Grapefruit juice—not an herbal remedy but a botanical product nonetheless—received considerable attention in the late 1990s as a proposed strategy to boost plasma saquinavir concentrations. While grapefruit juice does affect CYP3A4 activity in the intestines, it does not appear to cause clinically significant interactions with approved PIs or NNRTIs.

Herbal remedies and nutritional supplements are not closely regulated like drugs, and it is not always easy to determine the exact ingredients or

People with HIV should inform their health-care team (general practitioners, specialist physicians, nurses, alternative and complementary therapy providers) about all the medicinal products they are using: prescription drugs, OTC medications, recreational or street drugs, and alternative or complementary therapies including herbs and nutritional supplements.

amounts of various substances in these products. To reduce the risk of interactions, people with HIV should inform their health-care providers about any alternative or complementary therapies they are using or considering.

Conclusion

As aptly stated in the U.S. government's anti-HIV treatment guidelines, the list of interactions involving antiretroviral drugs is "extensive and constantly expanding," presenting a daunting challenge for HIV positive individuals and their providers.

The best way to minimize the risk of drug interactions is to remain vigilant. There is no need to memorize every possible interaction—even HIV/AIDS professionals find it difficult to keep up with the ever-growing list. Instead, become familiar with how drugs are metabolized, the major interaction mechanisms, and which drug classes are most likely to cause problems. With this background, refer to databases and tools like those listed in the sidebar on page 28. When considering a regimen change, do some research and ask about potential interactions. Pharmacists, who specialize in drugs and their pharmacokinetics, can be an excellent resource.

People with HIV should inform their health-care team (general practitioners, specialist physicians, nurses, alternative and complementary therapy providers) about all the medicinal products they are using: prescription drugs, OTC medications, recreational or street drugs, and alternative or complementary therapies including

herbs and nutritional supplements. Piscitelli recommends putting all these products in a bag and bringing them along to appointments so providers can see for themselves what their patients are using. He also emphasizes the importance of reviewing an individual's complete regimen at each visit. It is good practice to consider the possibility of a drug interaction if an antiretroviral regimen does not seem to be working as well as it should (e.g., rising viral load, decreasing CD4 cell count) or if a person experiences new, unusual, or severe side effects.

HIV positive people need not despair if they must take a medication implicated in many interactions. Often, drug interactions can be overcome simply by raising or lowering doses; however, this should never be done without the guidance of a knowledgeable practitioner. In other cases, it may be possible to replace an interacting drug with a noninteracting agent that works comparably well. Any time a new or unusual interaction comes to light, it should be reported promptly to the drugs' manufacturers and the FDA so that interaction databases can be updated and other people with HIV can benefit from this increasing body of knowledge.

Liz Highleyman (liz@black-rose.com) is a freelance medical writer and editor based in San Francisco.

Selected Sources

- Back, D. and others. Pharmacokinetic drug interactions with nevirapine. *Journal of Acquired Immune Deficiency Syndromes (JAIDS)* 34 (S1): S8–S14. September 2003.
- Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the

treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *Morbidity and Mortality Weekly Report* 49(09): 185–189. March 10, 2000.

De Luca, A. and others. Deep salvage with amprenavir and lopinavir/ritonavir: correlation of pharmacokinetics and drug resistance with pharmacodynamics. *JAIDS* 35: 359–66. April 20, 2004.

Dubé, M. and others. Preliminary guidelines for the evaluation and management of dyslipidemia in adults infected with human immunodeficiency virus and receiving antiretroviral therapy: recommendations of the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group. *Clinical Infectious Diseases* 31: 1216–1224. November 2000.

Elbekai, R. and others. The effect of liver cirrhosis on the regulation and expression of drug metabolizing enzymes. *Current Drug Metabolism* 5(2): 157–167. April 2004.

Fichtenbaum, C. and others. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG study A5047. *AIDS* 16: 569–77. March 8, 2002.

Haas, D. and others. A common CYP2B6 variant is associated with efavirenz pharmacokinetics and central nervous system side effects: AACTG Study NWCS214. 11th Conference on Retroviruses and Opportunistic Infections. San Francisco. February 8–11, 2004. Abstract 133.

Kashuba, A. and others. Combining fosamprenavir with lopinavir/ritonavir substantially reduces amprenavir and lopinavir exposure: ACTG protocol A5143 results. *AIDS* 19: 145–152. January 28, 2005.

Patel, I. and others. Pharmacokinetics, pharmacodynamics and drug interaction potential of enfuvirtide. *Clinical Pharmacokinetics* 44(2): 175–186. February 2005.

Pinzanni, V. and others. Methadone withdrawal symptoms with nevirapine and efavirenz. *Annals of Pharmacotherapy* 34: 405–407. March 2000.

Piscitelli, S. and Gallicano, K. Interactions among drugs for HIV and opportunistic infections. *New England Journal of Medicine* 344: 984–996. March 29, 2001.

Piscitelli, S. and others. Indinavir concentrations and St. John's wort. *The Lancet* 355(9203): 547–548. February 12, 2000.

Taburet, A. and others. Interactions between amprenavir and the lopinavir-ritonavir combination in heavily pre-treated patients infected with human immunodeficiency virus. *Clinical Pharmacology and Therapeutics* 75: 310–323. April 2004.

Vishnuvardhan, D. and others. Lopinavir: acute exposure inhibits P-glycoprotein; extended exposure induces P-glycoprotein. *AIDS* 17: 1092–1094. May 2, 2003.

von Moltke, L. and others. Protease inhibitors as inhibitors of human cytochromes P450: high risk associated with ritonavir. *Journal of Clinical Pharmacology* 38: 106–111. February 1998.

Wyles, D. and Gerber, J. Antiretroviral drug pharmacokinetics in hepatitis with hepatic dysfunction. *Clinical Infectious Diseases* 40: 174–181. January 1, 2005.