

What's in your medicine cabinet?

Interactions with HIV medications:

What HIV+ people should know

What are drug interactions?

HIV treatment usually involves 3 or more medications taken in combination. HIV+ people may also take additional meds to treat opportunistic infections (OIs) and other conditions associated with HIV/AIDS, or to manage drug side effects. As a result, drug interactions are possible between the HIV meds and these other kinds of meds. A drug interaction occurs when one med affects how the body processes or reacts to another med. This is true even for meds sold over-the-counter (OTC) without a doctor's prescription. Also, street drugs, methadone, alternative and complementary ("natural") therapies, and even certain foods may cause drug interactions with HIV meds. Some of these interactions have little effect, while others can lead to severe toxicities, loss of HIV suppression, or the emergence of drug-resistant virus.

What causes drug interactions?

Drug interactions fall into 2 broad categories: pharmacodynamic and pharmacokinetic. Pharmacodynamic interactions are those related to the combined activity of 2 or more drugs when used together. For example, sometimes the effects are additive or "synergistic," while other times the two drugs may be negative or "antagonistic." This can make either or both drugs more or less effective. Pharmacokinetic interactions occur when one agent changes the blood concentration of another.

PHARMACODYNAMICS: What a drug does to the body

PHARMACOKINETICS: What the body does to a drug

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 problems. For instance, individuals may possess genetic differences that affect expression of specific liver proteins (or "enzymes") used to process medications. One example of this includes the CYP450 enzymes in the liver.

The impact of liver disease is of special concern because a substantial proportion of HIV+ people have chronic hepatitis B or C co-infection, 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 than normal drug levels in the blood. The vast majority of drug interactions involving HIV meds are pharmacokinetic and the result of a change in the absorption, distribution, metabolism, or elimination of either the HIV medication itself or the concurrently administered medication.

How does this involve HIV meds?

Most of the HIV meds currently taken belong to one of the following families, 1) nucleoside reverse transcriptase inhibitors (NRTIs or "nukes"), 2) non-nucleoside reverse transcriptase (NNRTIs or "non-nukes"), and 3) protease inhibitors (PIs). The cytochrome P450 (CYP450) enzyme system is responsible for turning drugs from active to inactive metabolites that are excreted by the body. Both PIs and NNRTIs can affect the CYP450 system. Therefore, metabolic drug interactions are most common and problematic when prescribing combinations that include these kinds of HIV meds. Numerous isoenzymes in the CYP450 family have been identified, and those responsible for the elimination of the majority of HIV meds are CYP3A4, CYP1A2, and CYP2D6.

- **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. In the NRTI class of meds, only abacavir (Ziagen) is broken down by the same enzyme that metabolizes alcohol; so taking alcohol may raise abacavir levels.
- **NNRTIs**: All 3 approved NNRTIs affect the CYP450 system: nevirapine (Viramune) is a CYP3A4 inducer (making it process drugs more quickly), delavirdine (Rescriptor) is a CYP3A4 inhibitor (making it process drugs more slowly), and efavirenz (Sustiva) combines both effects. The NNRTIs also induce and/or inhibit other isoenzymes that play less important roles in drug interactions.
- **PIs**: As a class, the PIs 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 inhibitors than others and have additional side effects. In fact, ritonavir (Norvir) is known for its difficult side effects, but because it is a potent inhibitor of CYP450, it has since been used in low doses to achieve better levels of other PIs. This is the idea behind "boosted" PIs—now commonly done when people take PIs as part of their HIV combination therapy.

What about drugs used to treat OIs?

Several different kinds of meds may be used to treat OIs. The azoles, macrolides, and rifamycins can interact not only with HIV meds, but also with each other. Because of this complexity, the care of HIV+ people who require treatment for multiple OIs should be managed by experienced physicians.

How do acid-lowering drugs interact?

Medications that neutralize stomach acid can interfere with the absorption of drugs like atazanavir (Reyataz) that require an acid environment. Such medications are often taken to relieve acid reflux, or “heartburn.” OTC antacids (such as TUMS or Maalox) and buffered medications work for only a short time, making it possible to use them 1 to 2 hours after taking acid-dependent drugs. Other types of acid-lowering agents are much longer-acting. Proton pump inhibitors, which block the production of stomach acid, can alter gastric pH for 24 hours or longer. These include omeprazole (Prilosec), esomeprazole (Nexium), lansoprazole (Prevacid).

What if you are taking cholesterol-lowering medications?

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 Cardiovascular Disease Focus Group of the Adult AIDS Clinical Trials Group recommended that people on combination HIV therapy should start with low doses of pravastatin (Pravachol), atorvastatin (Lipitor), or fluvastatin (Lescol), which appear to interact least with HIV meds. The panel advised against use of lovastatin (Mevacor) or simvastatin (Zocor), which can reach dangerously high levels when used with PIs. Such high levels of statins might cause severe side effects including rhabdomyolysis (muscle damage) and kidney failure.

What about other meds?

PIs can increase blood levels of meds used to treat migraine headaches (ergot alkaloid derivatives such as Cafergot and Migranal), so coadministration of these drugs should be avoided. Levels of calcium-channel blockers (for example, Diltiazem and Verapamil) may also increase in the presence of CYP3A4 inhibitors (like PIs). These drugs are used to treat conditions such as angina (chest pain), high blood pressure, and cardiac arrhythmias.

PIs can also interact dangerously with immunosuppressive drugs such as tacrolimus (Prograf), which are used to prevent organ rejection after a transplant. Levels of the erectile dysfunction drugs sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis) may be increased when used with PIs, so a dose reduction of these drugs is recommended. In women using oral contraceptives containing ethynil estradiol or other forms of estrogen, concurrent use of efavirenz, nevirapine, nelfinavir (Viracept), ritonavir, or lopinavir/ritonavir (Kaletra) may decrease hormone levels—enough to cause unintentional pregnancies.

Recreational and Street Drugs

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. Other forms of amphetamine, including crystal meth (“speed,” “crank,” “Tina”), share the same processing pathway and may have similar interactions. However, cocaine, also a stimulant, has not been reported to interact with HIV meds. Ritonavir, other PIs, efavirenz, and nevirapine appear to reduce plasma concentrations of opiates (for example, heroin and numerous prescription pain-relievers), which may lead to withdrawal symptoms or inadequate pain relief.

Herbal Remedies

Herbal remedies and nutritional supplements are not closely regulated like medications, and it is not always easy to determine the exact ingredients or amounts of various substances in these products. To reduce the risk of interactions, people with HIV should inform their healthcare providers about any alternative or complementary therapies they are using or considering. A clear example of why this is important is the herbal remedy St. John’s wort, which is used to relieve depression. Studies have shown that St. John’s wort induces both CYP3A4 and P-glycoproteins (which help clear drugs out of cells in the body). This was associated with significantly decreased indinavir (Crixivan) concentrations in one study. Low levels of HIV meds can lead to the development of viral resistance to those meds. Garlic inhibits CYP3A4 activity, and a study showed that high-dose garlic supplements reduced saquinavir (Invirase) levels. Another herbal remedy that could interact pharmacokinetically with HIV med is milk thistle (and its derivative, silymarin). Also, while grapefruit juice does affect CYP3A4 activity in the intestines, it does not appear to cause major interactions with PIs or NNRTIs.

How can drug interactions be prevented?

People with HIV should inform their healthcare team (general practitioners, specialist physicians, nurses, and alternative/complementary therapy providers) about all the medicinal products they are using: prescription drugs, OTC meds, recreational or street drugs, and alternative or complementary therapies including herbs and nutritional supplements. When considering a regimen change, do some research and ask about potential interactions. Discuss potential interactions with your healthcare provider. Pharmacists, who specialize in drugs and their pharmacokinetics, can be also an excellent resource.

1407 Hawthorne
Houston, Texas 77006

713-527-8219

info@centerforaids.org
www.centerforaids.org



last updated October 2005