The issue of potential drug-drug interactions in HIV disease management was addressed at the Atlanta course by Charles W. Flexner, MD, from The Johns Hopkins University, in Baltimore, Maryland. Dr Flexner reviewed the definitions and mechanisms of inhibitors and inducers, discussed selected specific metabolic drug interactions, highlighted new information, and described some strategies in which some drug-drug interactions can be exploited to benefit HIV disease management.

Polypharmacy is a growing complication in HIV disease management. As the number of available drugs continues to increase, patients and physicians must deal with increasingly complex regimens and the increased risk of adverse drug interactions. The approved HIV protease inhibitors (saquinavir, ritonavir, indinavir, and nelfinavir) and the non-nucleoside reverse transcriptase inhibitors (NNRTIs; nevirapine and delavirdine) are especially susceptible to pharmacokinetic drug-drug interactions.

All of the protease inhibitors and NNRTIs are substrates for cytochrome P450 drug metabolizing enzymes, and primarily the 3A4 isomorph. The four approved protease inhibitors are also inhibitors of cytochrome P450 3A4. Ritonavir is by far the most potent inhibitor; nelfinavir and indinavir have intermediate potency; and saquinavir is the least potent inhibitor. The new soft gel capsule formulation of saquinavir results in higher drug concentrations, with additional potential for drug interactions. Delavirdine is a modest competitive inhibitor of the metabolism of some P450 substrates. Nelfinavir, nevirapine, and ritonavir are modest hepatic enzyme inducers.

Basic Pharmacology

A P450 substrate is any drug whose metabolism or biotransformation (chemical oxidation or reduction) is catalyzed by enzymes (isomorphs) in the cytochrome P450 family. These enzymes are called cytochromes because they contain a reactive metal ion (in this case iron) that serves as the ultimate electronic acceptor or donor in these chemical reactions.

There are at least 25 different cytochrome P450 isozymes in humans, but only a few of these enzymes are involved in drug metabolism. The 3A4 cytochrome is the major isomorph in HIV drug metabolism to date.

Inhibition

A P450 inhibitor is any drug that inhibits the metabolism or biotransformation of another drug catalyzed by enzymes in the cytochrome P450 family. Like most enzyme inhibition, P450 inhibition is competitive and reversible; once the inhibitor is withdrawn, the inhibition stops.

Ritonavir and delavirdine are P450 inhibitors that have very different effects on other drugs that are metabolized by these same enzymes. The inhibitory effects on selected drugs used in HIV infection are listed in Table 1. Delavirdine does not significantly affect ritonavir pharmacokinetics, but a dose adjustment of ritonavir may be required when it is combined with indinavir or saquinavir.

Unfortunately, it is not possible to precisely predict the magnitude of effect of one P450 inhibitor on another P450 substrate. It will be necessary to assess the individual effects in clinical studies.

There has been controversy about the role of grapefruit juice as an inhibitor of drug metabolism. Grapefruit juice contains a flavonoid, the complex

### Table 1. Selected P450 Enzyme Inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Effect</th>
<th>Interactions</th>
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| Ritonavir  | Increases | rifabutin AUC by 350%  
|            |         | 25-desacetyl rifabutin AUC by 3500%  
|            |         | clarithromycin AUC by 77%  
|            |         | trimethoprim AUC by 20%  |
| Delavirdine| Increases | indinavir AUC by 50%  
|            |         | saquinavir trough (Cmin) by 560%  |
| Amprenavir | Increases | rifabutin trough, (Cmin) by 3- to 6-fold  
|            |         | erythromycin AUC by the same amount as ketoconazole (270% increase in unmetabolized erythromycin)  |
| Efavirenz  | Increases | nelfinavir AUC by 20%  |

AUC indicates area under the curve.
molecule naringenin, which is a potent cytochrome P450 inhibitor. Grapefruit juice increases the saquinavir area under the curve (AUC) by approximately 2-fold to 3-fold, similar to the magnitude of effect of ketoconazole or erythromycin on saquinavir, but not nearly the magnitude of effect that ritonavir has on saquinavir.

Grapefruit juice increases the saquinavir AUC by 2-fold to 3-fold, similar to the magnitude of effect of ketoconazole or erythromycin on the drug

The interaction is likely to involve the intestinal and hepatic cytochrome P450 3A4 systems; drugs can be metabolized by cytochrome P450 in the intestinal tract before they reach the liver.

There is one case of death reported in the literature that is possibly linked with this effect. After taking terfenadine and drinking large quantities of grapefruit juice, a man died suddenly and without explanation while mowing his lawn. However, the patient was also alcohol dependent and had a cardiomyopathy. Staggering the grapefruit juice and the drug is being considered as a way to reduce this interaction. According to Dr. Flexner, it is conceivable that having patients who drink grapefruit juice wait for some period of time (eg, 2 hours) before taking saquinavir or indinavir might avoid this interaction, but the issue requires further study.

There are several agents that are involved in potentially serious metabolic drug interactions (Table 2). The use of these drugs should be avoided by patients taking P450 inhibitors, including HIV protease inhibitors and delavirdine.

**Induction**

A P450 inducer is a drug that causes increased production of enzymes responsible for the metabolism or biotransformation of another drug. In contrast to inhibition, induction reduces rather than increases drug concentrations. The inducer acts directly as a transcriptional transactivator, binding directly to regulatory regions in the DNA upstream from the genes that encode the drug-metabolizing enzymes and increasing transcription of those genes. Because the process of induction has a functional half-life of approximately 3 days, the effect is not immediately reversible when the drug is withdrawn. It takes approximately 2 weeks before enzyme levels return to predrug administration levels after stopping an inducer.

Table 3 lists the induction effects associated with selected drugs. Ethinyl estradiol, a synthetic estrogen component in most oral contraceptives, and zidovudine are metabolized by different pathways. Ethinyl estradiol is metabolized via cytochrome P450, and zidovudine is metabolized through hepatic glucuronidation transferase. Because ritonavir is a more ubiquitous molecular promoter/inducer, it has about the same effect on both drugs. Ritonavir increases P450 drug metabolism and increases other drug metabolizing enzymes in the liver.

While the inhibitors have a broad variety of effects on other drugs, the inducers have a predictable and consistent magnitude of effect for any given enzyme. Also, an inducer may exert an effect on more than one class of enzymes, such as P450 enzymes and glucuronidyl transferases affected by ritonavir.

Dr. Flexner and colleagues studied the relative effect of rifampin and rifabutin on the pharmacokinetics of oral contraceptives containing ethinyl estradiol and norethindrone. As P450 inducers, rifampin and rifabutin can accelerate clearance of both components.

<table>
<thead>
<tr>
<th>Table 2. Selected Agents Involved in Potentially Serious Drug-Drug Interactions With Protease Inhibitors</th>
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<tbody>
<tr>
<td>• Terfenadine, astemizole, cisapride</td>
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<tr>
<td>• Ergot alkaloids</td>
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<tr>
<td>• Midazolam, triazolam</td>
</tr>
<tr>
<td>• 3,4-methylenedioxyamphetamine* (MDMA; also known as Ecstasy)</td>
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<td>*Anecdotal evidence</td>
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<table>
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<tr>
<th>Table 3. Selected P450 Enzyme Inducers</th>
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<tr>
<td>Ritonavir reduces ethinyl estradiol AUC by 40%</td>
</tr>
<tr>
<td>zidovudine AUC by 25%</td>
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<tr>
<td>theophylline AUC by 43%</td>
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<tr>
<td>Nevirapine reduces indinavir AUC by 28%</td>
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<tr>
<td>saquinavir-HGC AUC by 27%</td>
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<td>Efavirenz reduces amrenavir AUC by 26%</td>
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<td>saquinavir-SGC AUC by 60%</td>
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AUC indicates area under the curve; HGC indicates hard gel capsule.
There have been anecdotal reports of unplanned pregnancies in oral contraceptive users who were taking rifampin. In a randomized, double-blind, placebo-controlled, cross-over trial with 12 women, administration of rifampin decreased the ethinyl estradiol AUC by 64%, compared with 34% for rifabutin. Administration of rifampin decreased the norethindrone AUC by 49% compared with a reduction of 12% for rifabutin. Despite this substantial pharmacokinetic effect, ovulation was still fully suppressed in all 12 women taking either drug in combination with their oral contraceptives. Thus, a statistically significant pharmacokinetic interaction may not always result in clinically significant consequences.

New Issues in Drug Interactions

Recently presented data indicate that efavirenz (DMP 266), an investigational NNRTI, and amprenavir (VX-478), an investigational protease inhibitor, have the potential to be involved in some clinically significant drug interactions. Efavirenz appears to be both a modest P450 inhibitor and inducer, and amprenavir is a modest P450 inhibitor (Tables 1 and 3).

Strategies for Avoiding or Capitalizing On Drug Interactions

In the future, based on a better understanding of pharmacology, new drugs that avoid interactions will likely be developed, and new combinations that take advantage of drug interactions, or that circumvent interactions, may be utilized.

For example, fexofenadine is a non-sedating antihistamine that was developed to avoid drug interactions. A dose of terfenadine is almost immediately converted in the liver to fexofenadine. Giving fexofenadine directly avoids the cardiac arrhythmias associated with terfenadine, the parent compound. If terfenadine is combined with a P450 inhibitor, conversion to fexofenadine is blocked and terfenadine concentrations increase, in some cases causing sudden death. Fexofenadine is the active metabolite of terfenadine. This metabolite is orally bioavailable and is not cardiotoxic. It is also clinically effective, and it is not apparently susceptible to adverse drug interactions.

Combined drug administration may take advantage of beneficial pharmacokinetic drug interactions. Benefits include improving bioavailability through inhibition of first-pass metabolism, reducing clearance to allow less frequent drug administration, increasing concentrations of active drug metabolites, and displacing highly protein-bound drugs from plasma protein binding sites. Treatment regimens employing dual protease inhibitor combinations may take advantage of such interactions and are currently under investigation.

The figure illustrates the pharmacokinetic enhancement of the indinavir

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**Figure.** Steady-state indinavir plasma profile. Gray line indicates administration of indinavir 800 mg every 8 hours under fasting conditions. Red line indicates administration of indinavir 400 mg/ritonavir 400 mg every 12 hours taken with regular meals.

Adapted and used with permission from Abbott Laboratories.
800 mg every-8-hours concentration time profile by combining it with ritonavir. A reduced dose of indinavir (400 mg every 12 hours) combined with ritonavir 400 mg every 12 hours results in a 10-fold increase in the trough concentration of indinavir during a 24-hour dosing interval. A reduction in the indinavir peak concentration may be advantageous with respect to the formation of kidney stones, although further study is required. This combination may have the advantages of improved convenience and relative cost-effectiveness.

The combination ritonavir/saquinavir is currently the most well-studied dual protease inhibitor regimen, and it has been suggested that the combination has two-dimensional synergy. Dr Flexner presented information on nelfinavir/ritonavir, which he noted to have the potential for three-dimensional synergy. The drugs select nonoverlapping primary resistance mutations and have a beneficial pharmacokinetic interaction. Nelfinavir, unlike the other protease inhibitors, makes an active metabolite, M-8, which in vitro appears to have antiretroviral activity similar to nelfinavir. Ritonavir may inhibit M-8 clearance to a greater extent than it does nelfinavir clearance. Finally, both drugs are highly protein-bound, especially to alpha-1 acid glycoprotein; one drug may displace the other from its protein binding sites and transiently increase free-drug concentrations.

Preliminary data from studies with ritonavir 400 mg twice daily/nelfinavir 500 or 750 mg twice daily in patients who are protease inhibitor-naive show an approximate 100- to 1000-fold drop in plasma HIV RNA levels. Most patients had added nucleoside reverse transcriptase inhibitors (nRTIs) to their regimens at 16 weeks of therapy in order to achieve plasma HIV RNA levels below the 20 copies/mL threshold. In contrast, fewer patients taking ritonavir/saquinavir added nRTIs to achieve plasma HIV RNA levels below the 50 copies/mL limit.

**Summary**

Clearly, the potential for dangerous drug interactions exists in patients taking anti-HIV medications. However, as noted by Dr Flexner, the chemical and pharmacologic principles involved are simple, only a few pharmacokinetic drug interactions are clinically significant, and some of these interactions may be clinically advantageous.

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### Suggested Reading


