Perspective

Drug-Drug Interactions and the Pharmacotherapy of HIV Infection

Angela D. M. Kashuba, PharmD

Knowledge of drug-drug interactions is crucial to HIV therapeutics. Recent reports in this area include reduced atazanavir exposure with coadministration of omeprazole or rifampin; increased hepatic toxicity with coadministration of saquinavir and rifampin; reduced buprenorphine exposure with concurrent efavirenz administration; absence of clinically significant interactions of depomedroxyprogesterone with nevirapine, efavirenz, or nelfinavir; increased atazanavir and saquinavir exposure with the double-boosted regimen of atazanavir/saquinavir/ritonavir; reduced amprenavir, lopinavir, and saquinavir exposure with the addition of tipranavir/ritonavir therapy, and reduced lopinavir and amprenavir exposure with the addition of fosamprenavir or fosamprenavir/ritonavir to lopinavir/ritonavir. This article summarizes a presentation on drug-drug interactions in HIV therapeutics by Angela D. M. Kashuba, PharmD, at the International AIDS Society–USA course in Los Angeles in April 2005.

Identical doses of a given drug do not necessarily produce the same plasma concentrations in patients because of genetic and environmental differences in absorption, distribution, metabolism, and excretion. Differences in drug pharmacokinetics may result in differences in pharmacodynamics, augmenting or diminishing the therapeutic or adverse effects of a drug. Drug-drug interactions are one of the factors that can exacerbate pharmacokinetic variability, along with drug-food interactions, drug-disease interactions (eg, due to alterations in gastrointestinal, renal, and hepatic function), and sex differences in drug pharmacokinetics, including those associated with pregnancy. Understanding drug interactions is crucial to the management of patients with HIV disease, given the multiple antiretroviral agents that must be taken and the use of other medications for HIV-related and non-HIV-related conditions. Recent findings on drug-drug interactions in HIV therapy are summarized herein.

Atazanavir/Ritonavir and Saquinavir/Ritonavir

Omeprazole

A recent study of 48 HIV-uninfected subjects indicated that coadministration of omeprazole 40 mg with atazanavir 300 mg/ritonavir 100 mg markedly reduced atazanavir trough plasma concentrations (C_trough) (Figure 1, Agarwala et al, 12th CROI, 2005). The effect of omeprazole was not countered by increasing the atazanavir dose to 400 mg or ingestion of 8 oz of cola to produce an acidic gastric/duodenal environment. Omeprazole concentrations were not significantly altered. It is currently recommended that the 2 drugs not be coadministered. One alternative acid-suppressing agent that could be used with atazanavir is famotidine. Recently presented data (Agarwala et al, 6th Int Workshop on Clin Pharmacol of HIV Ther, 2005) suggest that the atazanavir/famotidine interaction can be overcome by increasing doses or temporal dose separation. To achieve atazanavir systemic concentrations similar to those seen with a dose of 400 mg once daily, famotidine administration should be separated by at least 10 hours, or atazanavir should be given with ritonavir at a dose of 300 mg/100 mg once daily. To achieve exposures equivalent to those seen with an atazanavir/ritonavir regimen of 300 mg/100 mg once daily, the atazanavir dose could be increased to 400 mg.

Rifampin

In a study of 71 HIV-uninfected subjects, coadministration of rifampin and

Figure 1. Effect of omeprazole on atazanavir trough concentrations in HIV-uninfected subjects. Adapted with permission from Agarwala et al, 12th CROI, 2005.
As a percent of pre-efavirenz values, (McCance-Katz et al, 12th CROI, 2005). Decrease in buprenorphine exposure resulted in an approximate 50% reduction in buprenorphine exposure during treatment with efavirenz for 15 days in patients receiving buprenorphine, indicating the potential for antiretroviral agents on depomedroxyprogesterone efficacy. The potential for interactions of depomedroxyprogesterone with other PIs and with tenofovir needs to be evaluated.

Efavirenz and Buprenorphine

Buprenorphine is a partial opioid agonist recently approved for treatment of opioid tolerance. In a study of HIV-uninfected patients receiving buprenorphine, treatment with efavirenz for 15 days resulted in an approximate 50% decrease in buprenorphine exposure (McCance-Katz et al, 12th CROI, 2005). As a percent of pre-efavirenz values, post-efavirenz values for buprenorphine were 51% for area under the concentration-time curve (AUC) over 24 hours, 55% for maximum concentration (Cmax), 49% for minimum concentration (Cmin), and 72% for half-life. Efavirenz concentrations were within the therapeutic range. There was no change on the opiate withdrawal scale after 15 days; however, the long half-life of buprenorphine may have precluded seeing pharmacodynamic changes over this short time frame. This pharmacokinetic interaction is similar to that seen in studies of efavirenz and methadone. In these studies, symptoms of withdrawal were observed only after 3 to 4 weeks. Based on the currently available data, patients receiving efavirenz and buprenorphine should be closely monitored for symptoms of withdrawal.

Antiretrovirals and Depomedroxyprogesterone

Evaluation of changes in antiretroviral drug exposure in women receiving depomedroxyprogesterone showed little effect over 4 weeks. AUC0-12h values over 24 hours before and after depomedroxyprogesterone administration were 10.98 and 11.14 ng•h/mL for nevirapine (P=0.048), 3.56 and 3.50 ng•h/mL for efavirenz (P=not significant [NS]), 10.29 ng•h/mL for nelfinavir (P=NS), and 8.78 and 8.84 ng•h/mL for the active M-8 nelfinavir metabolite (P=NS, Cohn et al, 12th CROI, 2005). The small change in nevirapine exposure, although statistically significant, is likely not clinically significant. There was no evidence of ovulation over the short duration of the study, and none of the women became pregnant. However, the study was not powered to test the effects of antiretroviral agents on depomedroxyprogesterone efficacy. All PIs are metabolized by (ie, are substrates for) the cytochrome P450 (CYP450) enzymes; some PIs and some nonnucleoside reverse transcriptase inhibitors (NNRTIs) inhibit particular CYP450 enzymes, some induce CYP450 enzymes, and some both inhibit and induce these enzymes. Pharmacokinetic interactions may be difficult to predict based on the relative magnitudes of inhibition and induction reported from in vitro studies. Further, in vitro studies may be particularly inaccurate in characterizing enzyme induction, since they may measure responses of enzymes removed from intact cell systems. Lopinavir and ritonavir are metabolized by the CYP3A4 enzyme, and the anticonvulsant phenytoin is an inducer of CYP3A4; coadministration would thus be predicted to result in decreased lopinavir and ritonavir levels. Phenytoin is metabolized via the CYP2C9 and CYP2C19 enzymes, and lopinavir/ritonavir is reported to be an inhibitor of both enzymes; coadministration would thus be expected to result in increased phenytoin levels. In a study in which lopinavir/ritonavir and phenytoin were coadministered, lopinavir AUC and Cmax were reduced by 53% and 46%, respectively; ritonavir AUC and Cmax were reduced by 28% and 47%, respectively; and phenytoin AUC and Cmax were reduced by 31% and 34%, respectively. The reduction in phenytoin levels was an unexpected finding (Lim et al, J Acquir Immune Defic Syndr, 2004). Subsequent

Figure 2. Effect of rifampin on atazanavir trough concentrations in HIV-uninfected subjects. Adapted with permission from Burger et al, 12th CROI, 2005.

Atazanavir 300 mg/ritonavir 100 mg reduced atazanavir exposure, with the reduction again not being countered by an increase in the atazanavir and ritonavir doses to 400 mg and 200 mg, respectively (Figure 2; Burger et al, 12th CROI, 2005). Coadministration of atazanavir/ritonavir and rifampin should be avoided.

With regard to rifampin and other boosted protease inhibitors (PIs), a recent Dear Doctor letter described increased hepatotoxicity with coadministration of rifampin 600 mg once daily and saquinavir 1000 mg/ritonavir 100 mg twice daily. Elevated liver enzymes (up to 5-fold changes) were detected in 40% of the HIV-seronegative subjects evaluated. The mechanism of the liver toxicity is currently being investigated. It is recommended that saquinavir/ritonavir and rifampin not be used together.

PI Cytochrome P450 Inhibition and Induction: Lopinavir/Ritonavir and Phenytoin

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investigation of the effects of lopinavir/ritonavir in non-HIV-infected volunteers showed that in vivo lopinavir is an inducer of CYP2C9 (approx 25% increase) and CYP2C19 (approx 75% increase; Yeh et al, 5th Int Workshop on Clin Pharmacol of HIV Ther, 2004).

**Double-Boosted PIs**

**Atazanavir/Ritonavir Plus Saquinavir**

There is considerable interest in using 2 PIs with pharmacokinetic boosting from ritonavir—for example, to increase PI levels in patients with prior extensive treatment so that each PI might retain activity against virus resistant to the other PI. Such a strategy entails investigation of the pharmacokinetic interactions of the drugs considered for use. In one study, 40 patients received atazanavir 300 mg/ritonavir 100 mg daily plus saquinavir 1000 mg twice daily, 50 received atazanavir 300 mg/ritonavir 100 mg daily plus an nRTI twice daily, and 100 received saquinavir 1000 mg/ritonavir 100 mg twice daily plus an nRTI twice daily (Von Hentig et al, XV Int AIDS Conf, 2004). It was found that the addition of saquinavir significantly increased the Cmin of atazanavir, compared with that of atazanavir/ritonavir, and that the AUCs of both atazanavir and saquinavir significantly increased with the double-boosted regimen, compared with the single-boosted regimens. Sex and coadministration of tenofovir did not appear to have any effect on atazanavir AUC at steady state. The double-boosted regimen of atazanavir/ritonavir plus saquinavir at full therapeutic doses thus does not appear to have detrimental pharmacokinetic interactions.

**Tipranavir/Ritonavir**

In contrast, it was found in one study that adding PIs to a tipranavir 500 mg/ritonavir 200 mg regimen results in a detrimental interaction among the PIs. As shown in Figure 3, the AUC, Cmax, and Cmin of ritonavir-boosted amprenavir, lopinavir and saquinavir decreased markedly with the addition of tipranavir (Walmsley et al, XV Int AIDS Conf, 2004). This effect was not expected on the basis of the effects of tipranavir/ritonavir on hepatic CYP3A enzyme activity. The mechanism of the interaction is unclear, although it may relate to the effects of tipranavir on drug transporter activity, or a physical incompatibility of drugs in the gut.

**Lopinavir/Ritonavir Plus Fosamprenavir**

The A5143 study of lopinavir/ritonavir and fosamprenavir was the first evaluation intended to prospectively assess the efficacy of a double-boosted PI regimen compared with 2 single-boosted PI regimens. However, in a pharmacokinetic substudy, a significant interaction among the drugs was found, resulting in discontinuation of the study (Kashuba et al, AIDS, 2005; Wire et al, 11th CROI, 2004). As shown in Table 1, marked reductions in lopinavir and amprenavir AUC values

<table>
<thead>
<tr>
<th>Regimen/parameter</th>
<th>Lopinavir</th>
<th>Amprenavir</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>AUC0-12h</td>
<td>C12h</td>
</tr>
<tr>
<td>Lopinavir/ritonavir dose (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control1</td>
<td>400/100 bid</td>
<td>93 (µg•h/mL)</td>
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<tr>
<td>Lopinavir/ritonavir +fosamprenavir</td>
<td>400/100 bid</td>
<td>48 (µg•h/mL)</td>
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<tr>
<td>Geometric mean ratio1</td>
<td>0.52</td>
<td>0.39</td>
</tr>
<tr>
<td>Geometric mean ratio2</td>
<td>400/100 bid</td>
<td>1.37</td>
</tr>
<tr>
<td>Geometric mean ratio2</td>
<td>533/133 bid</td>
<td>0.95</td>
</tr>
</tbody>
</table>

1Kashuba et al, AIDS, 2005
2Wire et al, 11th CROI, 2004

AUC0-12h indicates area under the concentration-time curve from 0 to 12 hours; C12h, 12-hour concentration; bid, twice daily.
were observed with concomitant administration of lopinavir 400 mg/ritonavir 100 mg twice daily and fosamprenavir 700 mg twice daily. Boosting fosamprenavir 700 mg with ritonavir 100 mg twice daily resulted in increased lopinavir concentrations but not increased amprenavir concentrations. Increasing the lopinavir/ritonavir dose to 533 mg/133 mg twice daily and the fosamprenavir dose to 1400 mg twice daily brought lopinavir concentrations to control values, but amprenavir concentrations remained reduced. Additionally, this regimen was associated with significant toxicity. In another strategy to overcome what might be physical incompatibility of the 2 agents in the gut, lopinavir 800 mg/ritonavir 200 mg and fosamprenavir 1400 mg/ritonavir 200 mg were given once daily, 12 hours apart. Lopinavir exposure was similar to control values, but amprenavir exposure was still dramatically reduced (Corbett et al, 11th CROI, 2004). Data from the 56 patients enrolled in A5143 before the study was stopped indicated no significant differences between lopinavir/ritonavir plus fosamprenavir and lopinavir/ritonavir or fosamprenavir/ritonavir in virologic response rate (75% and 61%, respectively), CD4+ cell count response (increases of 81/µL and 41/µL, respectively), or reduction of plasma HIV RNA level to 50 copies/mL (54% and 46%, respectively, Collier et al, 12th CROI, 2005). Although the authors have concluded that the reduced drug exposure did not adversely affect response, since the hypothesis of the trial was that double boosting would improve virologic response, an adverse virologic effect of the interaction cannot be excluded.

### Tenofovir and Didanosine

Among nRTIs, there are interactions between tenofovir and didanosine despite the fact that they are not metabolized to active form via the same intracellular pathways. Tenofovir also has pharmacokinetic interactions with lopinavir/ritonavir, atazanavir, atazanavir/ritonavir, and tipranavir/ritonavir, indicating that nRTIs may sometimes affect metabolism of agents that are hepatically metabolized. Some of these may be occurring through transporter-mediated interactions. In the case of tenofovir and didanosine, coadministration has been found to increase didanosine AUC by 44% to 60%. The mechanism of interaction appears to involve the catabolic pathway for didanosine, in which the mutation (Staszewski et al, 44th ICAAC, 2004). An increased risk of hyperglycemia was observed in patients receiving tenofovir plus didanosine compared with those receiving only tenofovir or didanosine, with 60% of these patients receiving a reduced dose of didanosine (García-Benayas et al, 12th CROI, 2005). However, a poor immunologic response was not seen in a retrospective analysis of 219 patients treated with tenofovir plus didanosine, 89% of whom were receiving the 250 mg dose of didanosine (Karrer et al, 12th CROI, 2005).

![Figure 3. With-tipranavir to without-tipranavir ratio of amprenavir, lopinavir, and saquinavir area under the concentration-time curve (AUC), maximum concentration (C_{max}), and minimum concentration (C_{min}) for amprenavir/ritonavir, lopinavir/ritonavir, and saquinavir/ritonavir. Adapted with permission from Walmsley et al, XV Int AIDS Conf, 2004.](image-url)
Table 2. Pharmacology Information Resources

  (formerly www.hivatis.org)
- www.thebody.com
  (general information and news)
- www.iasusa.org
  (International AIDS Society–USA)
- www.hivinsite.org
  (University of California San Francisco)
- www.aidsmeds.com
- www.hivpharmacology.com

It has been hypothesized that the CD4+ cell decline with the tenofovir/ didanosine combination and the failure of triple-nRTI regimens including either tenofovir/didanosine or tenofovir/abacavir may be related to the effects on PNP (Kakuda et al, AIDS, 2004). PNP is involved in both the adenine and guanine metabolic pathways, in which it catalyzes the degradation of the purines to hypoxanthine and guanine. It is known that a hereditary deficiency in PNP is associated with increased deoxyguanosine triphosphate (dGTP) and deoxadename nosine triphosphate (dATP) levels, severe lymphopenia, and reduced T-cell number and function. Given the effect of tenofovir in inhibiting PNP and increasing didanosine concentrations, the questions have been posed whether (1) the lymphocyte toxicity observed with the full-dose combination is caused by PNP inhibition resulting in excess nucleotides; and (2) the failure of triple-nRTI therapy with tenofovir/abacavir/lamivudine and tenofovir/didanosine/lamivudine is related to imbalance in the deoxynucleotide triphosphate (dNTP) to deoxy nucleotide triphosphate (dNTP) pools as a result of PNP inhibition. These potential effects of PNP inhibition are currently being investigated.

Conclusion

The potential for drug interactions in the treatment of HIV infection and its complications is unprecedented. The virtually limitless number of drug combinations that may be taken by patients undergoing treatment of HIV infection makes pharmacokinetic and pharmacodynamic drug-drug interactions almost inevitable. This presentation reviewed some of the more recent pharmacology findings. Up-to-date information can also be found on the Web sites listed in Table 2, which also contain links to a large number of other resources.

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Suggested Reading


Kakuda TN, Anderson PL, Becker SL. CD4 cell decline with didanosine and tenofovir and failure of triple nucleoside/nucleotide regimens may be related. AIDS. 2004;18:2442-2444.


McCance-Katz EF, Pade P, Friedland G, Morse G, Moody D, Rainey P. Elavirenz decreases buprenorphine exposure, but is


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