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HEPP REPORT

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HIV & HEPATITIS
EDUCATION
PRISON
PROJECT

INFECTIOUS DISEASES IN CORRECTIONS

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ABOUT HEPP

HEPP Report, a forum for correctional problem solving, targets correctional physicians, nurses, administrators, outreach workers, and case managers. Published monthly and distributed by email and fax, HEPP Report provides up-to-the moment information on HIV/AIDS, hepatitis, and other infectious diseases, as well as efficient ways to administer treatment in the correctional environment. Continuing Medical Education credits are provided by the Brown University Office of Continuing Medical Education. HEPP Report is distributed to all members of the Society of Correctional Physicians (SCP) within the SCP publication, CorrDocs (www.corrdocs.org).

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CLINICALLY SIGNIFICANT DRUG INTERACTIONS ASSOCIATED WITH HIGHLY ACTIVE ANTIRETROVIRAL THERAPY

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One of the most challenging issues facing providers treating patients with human immunodeficiency virus - 1 (HIV) infection is the complex problem of drug interactions associated with highly active antiretroviral therapy (HAART). Guidelines for the initial treatment of HIV infection recommend the use of at least three antiretroviral medications, each of which is associated with significant drug interactions.¹ Further increasing the risk of drug interactions is the concurrent treatment of co-morbid disease states and therapies for prevention and/or treatment of opportunistic infections (OIs). This review focuses on the clinically significant drug interaction associated with the use of HAART.

DRUG INTERACTION OVERVIEW

Currently, there are 21 medications from four different classes licensed in the United States for the treatment of HIV infection. Drug interactions associated with HIV medications can be broadly classified into those that alter pharmacokinetics and those that alter pharmacodynamics.² Pharmacokinetic drug interactions generally result in a change in pharmacokinetic parameters, such as the area under the curve (AUC), which is a common measure of drug exposure, peak concentration (C_{max}), trough concentration, or half-life. Conversely, pharmacodynamic interactions result in alterations in the pharmacologic activity of the medication; generally not causing a change in pharmacokinetic parameters. The vast majority of drug interactions encountered in HIV medicine are pharmacokinetic in nature and occur as a result of a change in the absorption, distribution, metabolism or elimination of either the HIV medication itself or the concurrently administered medication.³

The cytochrome P450 (CYP450) enzyme system is responsible for the biotransformation of drugs from active to inactive metabolites that are readily excreted by the body. Given the effects of the protease inhibitor (PI) and non-nucleoside reverse transcriptase (NNRTI) class on the CYP450 system, metabolism drug interactions are most com-

mon and problematic when prescribing HAART. Though numerous isoenzymes of CYP450 have been identified, the enzymes responsible for the elimination of the majority of drugs used in HAART are CYP3A4, CYP1A2, and CYP2D6. Table 1 describes the route of elimination for HAART.

NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Drug interactions associated with the nucleoside (NRTI) and nucleotide (NtRTI) classes are minimal, as these medications are not metabolized by the CYP450 system. However, drug interactions may still occur within this class.

The currently available NRTIs and NtRTI include zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, emtricitabine, and tenofovir. Drug interactions with zidovudine are minimal; however, one of the few pharmacodynamic interactions encountered in HIV medicine occurs with co-administered zidovudine and stavudine. Since both of these NRTIs are thymidine analogues, they can compete for the same phosphorylation site in the growing chain of HIV DNA, resulting in an antagonistic, pharmacodynamic interaction.³ These two agents should therefore never be combined.

The use of didanosine (ddl) is often complicated by drug interactions. The buffered tablet formulation, which contains magnesium and calcium to improve systemic absorption, interacts with certain antibiotics.⁴ As a result of the buffer chelating the antibiotic, reduced ciprofloxacin, tetracycline or doxycycline absorption may occur. To minimize this interaction, ddl should be administered at

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CLINICALLY SIGNIFICANT DRUG INTERACTIONS...*(continued from page 1)*

least two hours after or six hours before the fluoroquinolone.⁵ Concurrent use of ddl-buffered tablet may also impair the absorption of the protease inhibitor (PI) atazanavir, since atazanavir requires an acidic environment for absorption.⁶ Patients should take a ddl-buffered tablet two hours after or one hour before taking atazanavir to minimize the interaction. Alternatively, use of the enteric-coated capsule formulation is an option; however, providers need to be sure that patients separate ddl and atazanavir since their dietary restrictions differ.^{6,7}

Probably the most significant ddl drug interaction reported occurs when didanosine is used concurrently with the NtRTI tenofovir. When enteric-coated ddl is co-administered with tenofovir, the ddl AUC increases by 60%.⁸ As a result, the recommendation for patients weighing >60kg who receive these medications concurrently is to reduce the ddl dosage to 250mg once daily. For patients weighing <60kg, no specific guidelines are available for ddl dosing; however, reduction to 200mg once daily is likely warranted. For severely underweight patients, providers may consider an even further ddl dosage reduction to 125mg once daily. Due to the magnitude of this interaction, all patients receiving concurrent tenofovir and ddl should be monitored closely for ddl-related toxicities such as pancreatitis, hyperlactatemia, and lactic acidosis, regardless of ddl dosage adjustments.

NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Three NNRTIs are currently licensed for use in the US: nevirapine, delavirdine, and efavirenz. Drugs in this class are prone to drug interactions, given the fact that they are extensively metabolized via CYP3A4 and can act as either inducers or inhibitors of CYP3A4. Nevirapine and efavirenz are, in general, inducers of CYP3A4, while delavirdine is an inhibitor of CYP3A4. When one of these agents is combined with a medication that is also metabolized by CYP3A4, a drug interaction is likely to occur.

Numerous drug interactions with nevirapine have been identified. Nevirapine is a CYP3A4 inducer, therefore most drug interactions associated with it lead to an increase in metabolism and reduced concentration of the co-administered drug. For example, when nevirapine is given concurrently with methadone, withdrawal symptoms may occur as a result of reduced methadone levels.⁹⁻¹² When using methadone and nevirapine concurrently, patients should be monitored closely for signs and symptoms of methadone withdrawal. Since the full effects of CYP3A4 induction may take time, signs of withdrawal may occur one to two weeks (or longer) after

TABLE 1: Routes of Elimination of Antiretroviral Agents and the Effect on CYP450

Drug	Elimination	Effect on CYP450 System
Zidovudine (AZT, ZDV)	Hepatic metabolism with renal excretion	None
Didanosine (ddl)	Renal excretion 50%	None
Zalcitabine (ddC)	Renal excretion 70%	None
Stavudine (d4T)	Renal excretion 50%	None
Lamivudine (3TC)	Renal excretion 70%	None
Tenofovir (TDF)	Renal excretion 70-80%	None
Abacavir (ABC)	Hepatic	Insignificant
Emtricitabine (FTC)	Renal excretion 86%	None
Nevirapine (NVP)	Hepatic	CYP3A4 inducer
Delavirdine (DLV)	Hepatic	CYP3A4 inhibitor
Efavirenz (EFV)	Hepatic	CYP3A4 inducer/inhibitor
Saquinavir (SQV)	Hepatic	CYP3A4 inhibitor
Ritonavir (RTV)	Hepatic	CYP3A4 inhibitor CYP2D6 inhibitor (3A4 inhibition >2D6) 3A4 and CYP1A2 inducer
Indinavir (IDV)	Hepatic	CYP3A4 inhibitor
Nelfinavir (NFV)	Hepatic	CYP3A4 inhibitor
Amprenavir (APV)	Hepatic	CYP3A4 inhibitor
Lopinavir/ritonavir (LPV/rvt)	Hepatic	CYP3A4 inhibitor CYP2D6 inhibitor (3A4 inhibition >2D6) 3A4 and CYP1A2 inducer
Atazanavir (ATZ)	Hepatic	CYP3A4 inhibitor, CYP1A2, CYP2C9 inhibitor
Fosamprenavir (FPV)	Hepatic	CYP3A4 inhibitor
Enfuvirtide (ENF)	Hepatic	None

Adapted from Reference 21.

nevirapine is added to methadone. An increase in methadone dosage may be necessary after the addition of nevirapine.

Concurrent nevirapine and oral contraceptive use may lead to contraceptive failure; therefore providers should recommend alternate methods of birth control.¹³ Rifabutin and rifampin are also potent CYP3A4 inducers and have been shown to reduce nevirapine trough concentrations by 16% and 37%, respectively. Therefore, patients on nevirapine who require anti-mycobacterial therapy should be given rifabutin to minimize the reduction in nevirapine drug levels.

Efavirenz is a potent inducer of CYP3A4 in vivo. As with nevirapine, CYP3A4 induction properties of efavirenz can result in reduced concentrations of concurrently administered drugs that are also metabolized by CYP3A4. In vitro data also suggest that efavirenz can inhibit CYP3A4. Efavirenz is therefore contraindicated with midazolam, triazolam, and ergotamine derivatives since there is a potential for increased drug concentrations of these medications and associated toxicity.¹⁴ Despite the inclusion of these contraindicated medications in the product labeling, no published case reports to date have either proven

or refuted the validity of these interactions. Concurrent use of the macrolide antibiotic clarithromycin should be avoided in patients receiving concurrent efavirenz. When used together, the clarithromycin AUC and C_{max} decreased by 39% and 26%, respectively.¹⁴ Therefore, clinicians may consider using azithromycin instead, as CYP450 drug interactions are unlikely with this medication.

Similar to nevirapine, methadone withdrawal has also been reported with concurrent use of efavirenz and methadone. This is more likely to occur when adding efavirenz to a stable methadone regimen.¹² Providers should be aware that the full effect of methadone withdrawal may take one to two weeks. Any change to antiretroviral therapy (ART) regimens should be communicated to methadone maintenance providers so that potential drug interactions may be anticipated and avoided.

Concurrent use of efavirenz with rifampin has been shown to reduce the AUC and C_{max} of efavirenz by 26% and 20%, respectively. Although the clinical significance of this interaction is unknown, providers should increase the efavirenz dosage to 800mg daily to offset this interaction when using rifampin to treat

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LETTER FROM THE EDITOR

Dear Colleagues:

Currently, there are twenty-one medications that have been FDA approved for the treatment of HIV infection. Most HIV-infected persons who have access to treatment are experiencing highly active antiretroviral therapy- (HAART) associated immune reconstitution, are less likely to develop an opportunistic infection or malignancy, and are living longer.

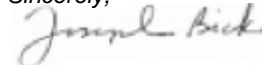
However, as we wade with our patients into this ever-growing pool of medications, the risks associated with polypharmacy have increased exponentially. Drug-drug interactions have been recognized that can lead to life-threatening toxicities or subtherapeutic medication levels. Clinicians who are not knowledgeable about these potential interactions can unwittingly contribute to the development of resistant strains of HIV. Alternatively, uninformed choices can lead to the failure of opportunistic infection prophylaxis or treatment.

The onus is therefore upon us as HIV care providers to be aware of the myriad of potential adverse interactions that accompany the medications in our armamentarium. In addition, we must be cognizant of interactions that may occur with over-the-counter drugs, herbal remedies, and recreational drugs. This month's lead article by Dr. John Faragon of Albany College of Pharmacy and Dr. Peter Piliero of Albany Medical College provides a thorough review of the clinically significant drug interactions associated with HAART. This month's HIV 101 addresses drug interactions that can occur with the concurrent use HAART and methadone.

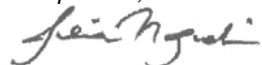
Next month we will bring you an update on Tuberculosis and a Spotlight on the growing role of electronic medical records in the management of chronic diseases, with a focus on products that are currently being used in the correctional setting.

As always, we welcome your feedback and suggestions. We value the collaborative relationship that we have developed with you, our readers and colleagues in correctional health care. It is our sincere hope that HEPP Report's first issue of 2004 meets your expectations, and that we continue to serve as a useful resource to you throughout the coming year.

Sincerely,



Joseph Bick, MD



Julia Noguchi, MA

FACULTY DISCLOSURE

In accordance with the Accreditation Council for Continuing Medical Education Standards for Commercial Support, the faculty for this activity have been asked to complete Conflict of Interest Disclosure forms. Disclosures are listed at the end of articles. All of the individual medications discussed in this newsletter are approved for treatment of HIV and hepatitis unless otherwise indicated. For the treatment of HIV and hepatitis infection, many physicians opt to use combination antiretroviral therapy which is not addressed by the FDA.

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tuberculosis.¹⁵ Another alternative would be to use rifabutin instead of rifampin; current guidelines suggest that the rifabutin dose be increased to 450 mg daily and the dosage of efavirenz should remain at 600mg once daily.

Unlike efavirenz and nevirapine, delavirdine is a potent inhibitor of CYP3A4. As a result, concurrent administration of drugs metabolized by the same isoenzyme are likely to cause increased drug levels and potential drug toxicity. Drugs that are likely to have increased serum levels when used concurrently with delavirdine include alprazolam, midazolam, triazolam, sildenafil, ergot alkaloid derivatives, nifedipine, and the HMGCoA-reductase inhibitors simvastatin and lovastatin.¹⁶ Concurrent use of these medications should be avoided in patients receiving delavirdine.

The medications rifampin and rifabutin have also been shown to reduce the AUC of delavirdine by 96% and 80%, respectively. Current guidelines for ART recommend that these medications be avoided in patients receiving concurrent delavirdine due to the high risk for development of resistance and virologic failure.^{15,16}

Other potential drug interactions with the entire NNRTI class include the anticonvulsants phenytoin, carbamazepine, and phenobarbital. Since these medications induce the CYP450 system, reduced drug levels of delavirdine, efavirenz, and nevirapine may occur and should be avoided if possible. A potential alternative is the medication levetiracetam and may be considered with concurrent ARV treatment, as it does not have significant CYP450 interactions. When prescribing levetiracetam, the patient should have close follow-up with a neurologist.

In treating patients who have failed their first regimen, or are in deeper salvage therapy, providers may be forced to use NNRTIs and PIs together. Providers need to be cognizant of dosage changes required when using these two classes concurrently, given the effect of both classes on the CYP3A4 system. As the NNRTIs efavirenz and nevirapine are known inducers of the CYP3A4 system, significant reductions in PI levels may occur when using these drugs concurrently. For example, when using efavirenz or nevirapine with indinavir or lopinavir/ritonavir, the AUC of the PIs are reduced by about 33%. To offset this interaction, providers need to increase the PI dosage: for indinavir the dosage needs to be increased to 1000mg every eight hours, and for lopinavir/ritonavir, the dosage needs to be increased to four capsules (533mg/133mg) twice daily.^{17,18} Conversely, as delavirdine is a potent inhibitor of CYP3A4,

TABLE 2: Dosing Recommendations when Combining Non Nucleoside Reverse Transcriptase Inhibitors and Protease Inhibitors

Protease Inhibitor/Non Nucleoside Reverse Transcriptase Inhibitor Combination	Dosage recommendation
Indinavir with efavirenz or nevirapine	Standard dose for efavirenz and nevirapine. Increase indinavir dosage to 1000mg every eight hours.
Indinavir with delavirdine	Standard dose delavirdine. Decrease indinavir dosage to 600mg every eight hours.
Amprenavir with efavirenz or nevirapine	Standard dose for efavirenz and nevirapine. Increase amprenavir dosage to 1200mg three times daily.
Lopinavir/ritonavir with efavirenz or nevirapine	Standard dose for efavirenz and nevirapine. Increase lopinavir/ritonavir dose to 533mg/133mg (four capsules) twice daily.
Atazanavir with efavirenz (and probably nevirapine, though dosages have not been established with nevirapine)	Standard dose for efavirenz and probably nevirapine. Give atazanavir 300mg once daily AND add ritonavir 100mg once daily
Fosamprenavir with efavirenz (and probably nevirapine, though dosages have not been established with nevirapine)	Standard dose for efavirenz and probably nevirapine. If using fosamprenavir with ritonavir twice daily, give fosamprenavir 700mg with ritonavir 100mg twice daily. If using fosamprenavir with ritonavir once daily, give fosamprenavir 1400mg with ritonavir 300mg once daily.

Data from references 17-21.

concurrent use with indinavir requires a dosage reduction to 600 mg every eight hours.¹⁷ No data exist that describe the pharmacokinetic interaction between lopinavir/ritonavir and delavirdine.

Concurrent use of the two new PIs atazanavir and fosamprenavir with either efavirenz or nevirapine also result in reduction in PI levels. However, instead of dosage adjustments, data suggest that the addition of ritonavir to these PIs is a viable option to offset the reductions in PI drug level. For example, during concurrent use of atazanavir and efavirenz, atazanavir AUC was reduced by about 74%.¹⁹ To offset the interaction, providers need to reduce the atazanavir dosage to 300mg once daily and also add ritonavir 100mg once daily. When boosted fosamprenavir once daily is used concurrently with efavirenz, fosamprenavir should be given 1400mg with 300mg of ritonavir once daily or fosamprenavir 700mg with ritonavir 100mg both twice daily.²⁰ Though data evaluating the drug interaction between nevirapine and either atazanavir or fosamprenavir are unavailable, expert opinion suggests that the same dosage adjustments should be made, given the similarity in efavirenz and nevirapine metabolism. Data combining these medications with delavirdine is not available. See Table 2 for a summary of dosage recommendations with select PI and NNRTI combinations.

PROTEASE INHIBITORS

All PIs are potent inhibitors of CYP3A4, and as a result, drug interactions are often very

complex. As a result of CYP3A4 inhibition, medication levels of agents also metabolized by the same isoenzyme have the potential to be markedly increased by the PI, potentially leading to an increased incidence of adverse effects. PIs have differing affinities for the CYP3A4 isoenzyme. The most potent inhibitor of CYP3A4 is ritonavir, whereas the least potent is saquinavir; CYP3A4 inhibition associated with indinavir, nelfinavir, and amprenavir, and atazanavir tends to be intermediate.²¹ Ritonavir is often the most likely medication in the PI class to cause drug interactions because in addition to its CYP3A4 inhibition, it also inhibits CYP2D6 and induces CYP1A2 and CYP2C9. However, ritonavir is often used to enhance the pharmacokinetic parameters of co-administered PIs due to its potent inhibition of their metabolism by CYP3A4.

Numerous medications should be avoided when using PI-based therapy. The benzodiazepines midazolam and triazolam are contraindicated, as these medications are metabolized by CYP3A4 and their concentrations can be markedly increased, resulting in prolonged sedation. Though the benzodiazepine alprazolam may also be increased by concurrent PI therapy, low doses may be acceptable to use. Other potential alternatives to these agents include lorazepam, oxazepam, or temazepam, as these medications are not metabolized by CYP450.²¹

Hyperlipidemia is a common occurrence with

CLINICALLY SIGNIFICANT DRUG INTERACTIONS...*(continued from page 4)*

PI therapy, though it may also be associated with stavudine and efavirenz. As a result, providers often treat hyperlipidemia with either fibric acid derivatives or with HMG-CoA reductase inhibitors, also referred to as statins. Although drug interactions with the fibric acid derivatives have not been identified, the use of certain statins is contraindicated with the use of a PI. The two most problematic statins are simvastatin and lovastatin, as these agents are extensively metabolized via CYP3A4.²² When used concurrently with PIs, these statin levels are markedly increased, placing the patient at risk for myopathy, rhabdomyolysis, and possibly renal failure and death. Statins that are considered safe include pravastatin or fluvastatin, as they have minimal effect on CYP450, therefore reducing the risk of drug interactions. Another potential option is atorvastatin, however CYP3A4 is involved with its metabolism. Use of atorvastatin with PI therapy should be done only with the lowest available dosages and with close follow-up for potential hepatotoxicity and muscle toxicity. The newest statin, rosuvastatin, cannot be recommended as no drug interaction studies exist evaluating concurrent PI use.

The use of PIs (and NNRTIs) often complicates the treatment of mycobacterial infections such as tuberculosis and MAC because rifampin and rifabutin are potent inducers of CYP3A4, leading to significant reductions in PI levels. However, rifampin is much more problematic, as it is a more potent inducer of CYP3A4 compared to rifabutin. Therefore, concurrent use of rifampin with PI regimens that do not include ritonavir is generally contraindicated due to risks of subtherapeutic levels of PIs that can result in either virologic failure or resistance.

Herbal therapy is common in the setting of HIV infection.²³ Oftentimes, herbal therapies have not been studied with concurrent HAART, and therefore their use should be discouraged unless data evaluating their effect on HAART are available. St. John's wort and garlic supplementation significantly reduce the levels of the PIs indinavir and saquinavir soft gel capsule, respectively.^{24,25} Since other PIs and NNRTIs are also metabolized by CYP3A4, similar interactions with other medications in these classes would be expected. Therefore, patients should be encouraged to avoid St. John's wort, garlic supplements, and other herbal therapies that have not been formally studied with PIs. The herbal therapy milk thistle, often used as a hepatoprotectant, has been shown to have minimal effects on the PI indinavir.²⁶ Providers choosing to offer milk thistle to patients may be able to do so safely with PI- and NNRTI-based therapies;

TABLE 3: Drugs to Avoid With PI-Based HAART Regimens

Drug	Interaction	Recommendation
Ergot alkaloids such as dihydroergotamine, ergonovine, ergotamine, methylethergonovine	Impaired hepatic metabolism from PI reported to increase risk of ergotamine toxicity	Avoid concurrent use with PI therapy. Consider alternative drugs such as sumatriptan.
Simvastatin, lovastatin, high dose atorvastatin	HMG CoA reductase inhibitor levels markedly increased	Select pravastatin or low dose atorvastatin during concurrent PI therapy as alternatives.
Phenytoin, carbamazepine, phenobarbital	Potential for increased metabolism of PI, leading to virologic failure	Avoid concurrent use if possible. Consider alternative anticonvulsant during PI therapy.
Alprazolam, midazolam, triazolam	Potential for prolonged or increased sedation or respiratory depression	Avoid concurrent use. Consider zolpidem or lorazepam.
GI motility agents	Cisapride	Contraindicated due to marked increase in cisapride levels and potential for QT prolongation
St. John's wort	Significant decrease in PI (IDV studied) levels, potentially leading to virologic failure or resistance	Avoid concurrent use during PI therapy.
Garlic	Significant decrease in PI (SQV studied) levels, potentially leading to virologic failure or resistance	Avoid concurrent use with PI therapy.
Pimozide	Potential increased risk of cardiac toxicity with concurrent ritonavir use	Avoid concurrent use with ritonavir-based regimens, including lopinavir/ritonavir.
Rifampin	Significant decrease in PI concentrations, potentially leading to virologic failure May use with full dose ritonavir	Consider rifabutin as an alternative.
Amiodarone, propafenone, bepridil, quinidine, flecainide	Potential increased risk for severe cardiac arrhythmias with concurrent ritonavir use	Avoid concurrent use with ritonavir-based regimens, including lopinavir/ritonavir.
Proton Pump Inhibitors such as omeprazole, esomeprazole, lansoprazole, rabeprazole, pantoprazole	Significant reductions in atazanavir plasma concentrations	Avoid concurrent use with atazanavir; consider use of an H2 receptor antagonist separated by at least 12 hours from atazanavir administration.

Adapted from reference 19, 21

however, data demonstrating its effect on PIs exist only for indinavir.

Drugs for erectile dysfunction, such as sildenafil, vardenafil and the recently approved tadalafil, can also have their levels increased significantly by concurrent PI use.²⁷⁻²⁹ Specifically, sildenafil levels can be increased from two to eleven-fold when used concurrently with PI therapy. Therefore, clinicians should prescribe, at most, 25mg every 48 hours initially. For patients who do not respond to 25mg, consideration for using higher doses should only be done with extreme caution. PIs can also increase vardenafil concentrations.

Current guidelines from the product labeling suggest that for patients on a PI-based regimen that does not include ritonavir, the maximum initial dose of vardenafil should be 2.5mg, without repeating the dose for 24 hours.²⁹ For patients receiving ritonavir even at low doses, the maximum initial vardenafil dose should be 2.5mg and should not be repeated for 72 hours.²⁹ Tadalafil was also recently approved; maximum doses used should not exceed 10mg every 72 hours for patients receiving concurrent PI therapy.³⁰ Possible toxicities from these drugs include priapism, hypotension, and visual color changes.

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CLINICALLY SIGNIFICANT DRUG INTERACTIONS...*(continued from page 5)*

HIV-infected patients may either have a seizure disorder or may require seizure prophylaxis due to OIs that involve the central nervous system. This often becomes problematic in the setting of HAART due to very limited data on concurrent use of anticonvulsants and PIs. Use of the anticonvulsants phenytoin, phenobarbital, and carbamazepine is of particular concern as they induce CYP450 enzymes that may lead to reduced PI or NNRTI levels.²¹ In fact, one case report in the literature describes ART failure possibly related to carbamazepine therapy in a patient receiving a PI.³¹ In this case, 200 mg of carbamazepine was taken with 800 mg of indinavir every eight hours, which led to subsequent virologic failure. Therefore, concurrent use of these drugs with PIs should be avoided, and a different anticonvulsant should be considered. More recently, a drug interaction study was reported between lopinavir/ritonavir and phenytoin.³² When used together, a dual interaction occurred, such that the levels of both lopinavir and phenytoin were markedly reduced. Therefore, providers should avoid this combination and select an alternative HAART regimen or an alternative anticonvulsant. One potential option is the use of levetiracetam, an anticonvulsant that has minimal drug interactions. Use of this medication in HIV-infected patients has not been studied, and therefore its use for treatment or prevention of seizures should only be done with close consultation with a neurologist. Whenever possible, patients who require concurrent HAART and anticonvulsant therapy should undergo periodic monitoring of anticonvulsant drug levels. For some PIs, therapeutic drug monitoring may also be an option to ensure that adequate levels are being attained. Consensus

trough concentrations have been established and are available in the most recent revision of the federal Department of Health and Human Services Guidelines.¹

Patients infected with HIV-1 may require antifungal therapy for such infections as cryptococcal meningitis, or candidiasis. With regard to PI drug interactions, the safest of the oral medications is fluconazole, as drug interactions are minimal.^{33,34} However, the azole antifungal ketoconazole is a potent CYP3A4 inhibitor and increases the level of drug exposure to saquinavir and amprenavir by 190% and 31%, respectively.^{35,36} Conversely, ritonavir and lopinavir/ritonavir have demonstrated a three-fold increase in ketoconazole levels when used concurrently. Therefore doses >200 mg/day of ketoconazole are not recommended when using these medications concurrently.¹⁸ In general, ketoconazole should be avoided with concurrent HAART. The newest azole antifungal, voriconazole, has significant activity against aspergillosis and candida albicans. Its use for treatment of candidiasis in HIV-infected patients has been established; however, drug interaction data only exist for concurrent use of indinavir, where no clinically significant interaction occurred.³⁷ Although extrapolation to other PIs may be possible, until data are available, use of this azole with other PI-containing regimens (especially those that contain ritonavir) should be undertaken when an alternative azole cannot be used, and with close monitoring for voriconazole toxicity, such as elevated transaminases and visual toxicity.

One of the recently approved PIs for use in the U.S. is atazanavir.¹⁹ Drug interactions with atazanavir are very similar to the other PIs; however, some differences do exist. In particular, atazanavir is a pH-dependent medication, requiring an acidic environment for

absorption. As a result, the use of drugs that may alter the gastric pH are likely to be problematic. Since antacids may reduce atazanavir absorption, atazanavir should be administered two hours before or one hour after antacids. Proton pump inhibitors (PPIs) such as lansoprazole and omeprazole significantly alter the gastric pH for prolonged periods of time (often lasting longer than 24 hours), the atazanavir product labeling recommends that PPIs should not be used concurrently with atazanavir. As an alternative, providers may consider the use of a once daily histamine-2 (H-2) receptor antagonist separated by 12 hours from atazanavir. The current thought is that H2 blockers provide less prolonged suppression of acid, and, if separated, the interaction should be minimized. However, no data exist to prove or refute this theory.¹⁹

Other significant drug interactions may also occur with concurrent PI use. Table 3 summarizes medications that should generally be avoided with concurrent PI therapy.

CONCLUSIONS

Drug interactions are often complex and may be difficult to predict due to limited studies. Providers should be diligent in educating themselves about routes of metabolism for HAART and commonly prescribed medications to help recognize potential medications that may be problematic. As therapy for HIV changes very rapidly, providers may utilize internet resources to help screen for potential drug interactions and to identify new treatment options and issues surrounding HIV infection (See Resources on p.8). With such interventions, toxicity or adverse events associated with drug interactions may be prevented.

DISCLOSURES: *Speakers fees : Abbott, Agouron (Pfizer), and GlaxoSmithKline, Consultant fees: Roche and Gilead

**Honoraria: BMS, Abbott, GSK, Roche, Merck, Gilead, Research: GSK, Roche, Trimeris, Pfizer, Boehringer-Ingelheim, Gilead

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Drug Interactions with HAART and Methadone

DRUG	EFFECT OF ANTIRETROVIRAL THERAPY ON METHADONE	EFFECT OF METHADONE ON ANTIRETROVIRAL THERAPY
NUCLEOSIDE/NUCLEOTIDE ANALOGUES		
Abacavir	Decreased methadone clearance 25%	Decreased abacavir peak concentration 34%
Didanosine, buffered tablet	Unknown	Decreased didanosine AUC 57%
Didanosine, enteric-coated capsule	Unknown	No significant change in didanosine AUC
Lamivudine	Unknown	No significant change when given as zidovudine-lamivudine
Stavudine	Unknown	Decreased stavudine AUC 23%
Tenofovir disoproxil fumarate	Unknown	No significant change in tenofovir DF
Zalcitabine	Unknown	Unknown
Zidovudine	Unknown	Increased zidovudine AUC 41%
NON NUCLEOSIDE ANALOGUES		
Delavirdine	Unknown, although potential increased methadone effect	No change in delavirdine or N-delavirdine
Efavirenz	Decreased methadone levels 57%	Unknown
Nevirapine	Decreased methadone levels 51%	Unknown
PROTEASE INHIBITORS (PIS)		
Amprenavir	Decreased methadone AUC 35%	Decreased amprenavir AUC, Cmax, Cmin
Indinavir	No significant change in methadone AUC	Insignificant change in indinavir AUC; increased indinavir Cmin 50%-100%; decreased indinavir Cmax 16%-36%
Lopinavir-ritonavir	Decreased methadone AUC 36%	Unknown
Nelfinavir	Decreased methadone AUC 40%	Decreased nelfinavir metabolite (M8) AUC 53%; clinical significance unknown
Ritonavir	Decreased methadone AUC 36%	Unknown
Saquinavir, hard-gel capsule	Unknown with saquinavir as sole PI	Unknown with saquinavir as sole PI
Saquinavir, soft-gel capsule	Unknown with saquinavir as sole PI; unbound methadone concentrations unchanged when using saquinavir and ritonavir concurrently	Unknown with saquinavir as sole PI; potential reduction in saquinavir Cmin when using saquinavir and ritonavir concurrently

AUC, area under the concentration time curve; Cmax, maximum drug concentration or peak level; Cmin, minimum drug concentration or trough level.

Drug Interactions Associated With HAART: Focus on Treatments for Addiction and Recreational Drugs. *AIDS Reader* 13(9):433-450, 2003. Available at www.medscape.com/viewarticle/461892_4

CLINICALLY SIGNIFICANT DRUG INTERACTIONS... (continued from page 6)

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SAVE THE DATES

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INSIDE NEWS

Rise in Syphilis Among MSM in San Francisco Linked to Internet

The internet is a major factor in San Francisco's increase in early syphilis infections among men who have sex with men (MSM), according to a recent study from the CDC. A focus on data for 415 MSM diagnosed with early syphilis in 2002 found that internet chat rooms were the most common venues for meeting partners. Last year, the city reported the highest rates of first and second-stage syphilis of any metropolitan area in the nation. Between 1998-2002, early syphilis cases increased from 41 to 495. Officials noted at the time the proportion of cases among MSM had jumped from 22 percent in 1998 to 88 percent in 2002. However, the CDC and San Francisco Department of Public Health officials say that they have evidence that internet-based partner notification can be an effective tool for finding and treating early syphilis infections.

"Internet Use and Early Syphilis Infection Among Men Who Have Sex with Men - San Francisco, California, 1999-2003," MMWR (2003;52(50):1229-1232).

Bioequivalence study: 500 mg pill of Invirase

Two 200 mg formulations of Saquinavir (SQV) are currently marketed for oral administration in the treatment of HIV infection: Invirase, a hard gelatin capsule (saquinavir mesylate) and Fortovase, a soft gelatin capsule (saquinavir base). Both formulations have shown good efficacy and safety when boosted with ritonavir (r) in a SQV/r dosing of 1000/100 mg bid. The pill count for a SQV/r regimen using the current 200 mg formulation is 12 pills per day. Roche is developing a 500 mg saquinavir mesylate tablet that is smaller than the existing 200 mg formulation, allowing the use of only two SQV tablets twice daily in combination with ritonavir. The lower pill count and improved convenience may improve adherence to SQV/r regimens.

Boffito, Marta et al 9th EACS, October 2003, Warsaw, Poland. Oral Abstract

Study: Safety, Tolerability, and Efficacy of Interferon/Ribavirin Combination Therapy in Methadone Maintenance (MM) Patients with Active Hepatitis C (HCV)

In this study from the University of California, 78 percent of MM treated patients completed the six to 12 month course of interferon/ribavirin combination therapy. The end-of-treatment virologic

response rate was 64% in patients completing treatment and 54% in an intent-to-treat analysis. Despite the fact that MM patients exhibit a number of factors that make HCV treatment challenging, such as older age, a higher prevalence of psychiatric illness, and more advanced liver disease, their end-of-treatment response rate to therapy is similar to that of patients without a history of IDU. These preliminary suggest that that MM patients should be considered as potential candidates for HCV treatment.

Sylvestre, DL. Treating Hepatitis C in Methadone Maintenance Patients: An Interim Analysis, Drug and Alcohol Dependence 67 (2) (2002) pp. 117 - 123.

Study: Gilead Announces Preliminary Results from 48-Week Phase III Study of Emtricitabine in Patients with Chronic Hepatitis B

Preliminary results from a Phase III clinical trial comparing the efficacy and safety of emtricitabine 200 mg once daily versus placebo in patients with chronic hepatitis B have been released. The results demonstrate improvements in liver histology in 62% of patients who received the drug compared to 25% of patients who received placebo (p less than 0.001). Improvement in liver histology was the primary endpoint in this study. Gilead expects to present these data in detail at a scientific conference next year.

www.natap.org 11/26/03

New CDC HIV Prevention Funding Emphasizes Effectiveness, Focuses on Those Already Infected

The federal Centers for Disease Control and Prevention (CDC) has announced \$49 million in HIV prevention grants that require grantees to prove that their efforts are effective and focus more on doing prevention among people who are already infected with the virus. "The announcement included some specific items that are called program performance indicators," said Dr. Harold W. Jaffe, director of CDC's National Center for HIV, STD and TB Prevention. "They attempt to set goals." The CDC expects to fund roughly 160 grants ranging in amounts from \$100,000 to \$500,000, according to the December 3, 2003 announcement. The grants will run for five years, but the \$49 million represents only the first year's funding.

HIV Update, 12/15/03

RESOURCES

www.hiv.medscape.com

New data from conferences, CE articles on HIV related topics and more.

www.aidsinfo.nih.gov

DHHS Guidelines for treatment of HIV infected adults, adolescents, children...

www.hivandhepatitis.com

Treatment/developments for Hepatitis A, B and C

and conferences/new journal articles related to HIV/AIDS.

www.hopkins-aids.edu

HIV clinical trials/developments and animation of viral life cycle that includes action of ART

www.hivguidelines.org

NYSDOH AIDS Institute Clinical Guidelines for adults, pediatrics, ART in adults, and more.

SELF-ASSESSMENT TEST FOR CONTINUING MEDICAL EDUCATION CREDIT

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1. The following two antiretroviral agents compete for the same phosphorylation site in the growing chain of HIV DNA, resulting in an antagonistic, pharmacodynamic interaction:

- (a) zidovudine and stavudine
- (b) zidovudine and didanosine
- (c) didanosine and stavudine
- (d) lamivudine and emtricitabine

2. The following antiretroviral agent contains magnesium and calcium and therefore interferes with the absorption of antibiotics such as ciprofloxacin, tetracycline and doxycycline.

- (a) zidovudine
- (b) didanosine
- (c) abacavir
- (d) tenofovir

3. Which of the following statements is true:

- (a) Nevirapine and efavirenz are, in general, inhibitors of CYP3A4, while delavirdine is an inducer of CYP3A4
- (b) when nevirapine is given concurrently with methadone, intoxication symptoms may occur as a result of increased methadone levels
- (c) When enteric-coated ddI is co-administered with tenofovir, the ddI AUC increases 60%.
- (d) Abacavir increases the metabolism of oral contraceptives and can lead to contraceptive failure; therefore providers should recommend alternate methods of birth control for patients receiving abacavir.

4. When used together with one of the following antiretrovirals, the AUC and Cmax of clarithromycin decreased 39% and 26%, respectively. Concurrent use of clarithromycin should therefore be avoided in patients receiving:

- (a) nelfinavir
- (b) efavirenz
- (c) lopinavir
- (d) abacavir

5. The concentrations of some "statins" are markedly increased by concurrent protease inhibitor therapy, placing the patient at risk for myopathy, rhabdomyolysis, and possibly renal failure and death.

Statins which are considered safe because of minimal cytochrome P450 interactions include:

- (a) lovastatin and atorvastatin
- (b) simvastatin and lovastatin
- (c) pravastatin and fluvastatin
- (d) lovastatin and pravastatin

6. When rifampin must be used for treatment of a mycobacterial infection, the following is an appropriate concurrent dose:

- (a) Nelfinavir 1250 mg p.o. bid
- (b) Indinavir 800 mg p.o. tid
- (c) Saquinavir 1200 mg p.o. bid
- (d) Efavirenz 800 mg p.o. qd

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