Managing Issues Related to Antiretroviral Therapy

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Antiretroviral regimens are complicated and difficult for patients to follow, and they can have serious side effects, such as osteonecrosis and bone demineralization. Protease inhibitor therapy has been associated with hyperlipidemia, hyperglycemia, gastrointestinal symptoms, and body-fat distribution abnormalities. Nonnucleoside reverse transcriptase inhibitors can cause rashes and hepatotoxicity, and nucleoside reverse transcriptase inhibitors can cause lactic acidosis, hypersensitivity reactions, neuropathies, pancreatitis, anemia, and neutropenia. Malabsorption can occur if antiretroviral agents are taken improperly with regard to meals or if they are taken with certain other drugs or herbal remedies. Some commonly prescribed drugs can cause dangerous drug toxicities if they are taken by patients who are also taking certain antiretroviral medications. Suboptimal exposure to antiretrovirals because of noncompliance or malabsorption can result in viral resistance and loss of future treatment options. (Am Fam Physician 2003;68:675-86,689-90.

A patient information handout on antiretroviral therapy, written by the authors of this article, is provided on page 689.

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See page 621 for definitions of strength-of-evidence levels.

The effectiveness of highly active antiretroviral therapy regimens has changed the natural history of human immunodeficiency virus (HIV) infection.[1,2] HIV-related deaths and opportunistic infections have decreased dramatically, and health care providers are focusing on management of increasingly complex drug regimens and their associated interactions and toxicities.[1-3]

Advisory panels recommend that experts care for HIV-infected patients.[4,5] However, as the population of survivors living with acquired immunodeficiency syndrome (AIDS) increases and most of their health care delivery shifts from the inpatient to the outpatient arena, family physicians are likely to be confronted by an increasing array of HIV-related health issues, such as side effects of antiretroviral medications, drug interactions, and patient adherence to treatment regimens.[1,6]

Side Effects of Antiretroviral Drugs

Antiretroviral drugs used in HIV management fall into three major classes: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). A nucleotide reverse transcriptase inhibitor (NtRTI), tenofovir (Viread), and a newly approved fusion inhibitor, enfuvirtide (Fuzeon), also are available. The protease inhibitors have the most side effects and strictest dosing regimens. *Tables 1 through 4*[7-11] summarize the properties of antiviral drugs currently approved for treatment of HIV infection.

The U.S. Food and Drug Administration recently approved three new drugs for treatment of HIV infection. Enfuvirtide represents the first new class of drug approved for HIV treatment in seven years. It works by a different mechanism than all previous classes, inhibiting the fusion of HIV-1 with CD4+ T lymphocytes.[12] The production process is far more complicated than that of other antiretrovirals, making the wholesale cost of the drug approximately $20,000 per patient per year.[12] Enfuvirtide is approved only for use in patients with drug-resistant HIV infection.

The second new drug, atazanavir (Reyataz), is the first once-daily protease

Monitoring fasting glucose levels is useful in patients taking protease inhibitors because of the potential for developing glucose intolerance, insulin resistance, and type 2 diabetes.

inhibitor. It may have little to no adverse impact on serum lipid levels and possibly none on lipodystrophy.[13,14]

Emtricitabine (Emtriva) is an NRTI that was approved for treatment of HIV infection in July 2003.[15] As with atazanavir, its once-daily dosing regimen may increase compliance.

METABOLIC EFFECTS

Abnormal accumulation of body fat with truncal gain and peripheral loss; insulin resistance; and elevated cholesterol, triglyceride, and glucose levels can occur with the use of PIs. Retrospective analyses have offered conflicting evidence about whether antiretroviral agents increase the risk of coronary artery disease.[16,17] When intervention is indicated, a lipid-management program emphasizing dietary adjustments should be implemented. Because of the potential for substantial toxicity, the dosages of antihyperlipidemic agents should be reduced when they are taken with PIs.

Ritonavir (Norvir) increases serum levels of simvastatin (Zocor) and can cause myalgias, rhabdomyolysis, renal failure, and liver damage. PIs should not be used concurrently with simvastatin or lovastatin (Mevacor); pravastatin (Pravachol) is the safest statin to use with PIs.[7] Because of the potential for enhanced statin-related toxicity, atorvastatin (Lipitor) and fluvastatin (Lescol) should be used with caution and in lower dosages when taken with PIs.[7]

Serum lipid abnormalities have resolved in some patients after discontinuing PI therapy and starting PI-sparing regimens.[1] However, this step requires a risk-benefit analysis in consultation with an infectious disease or HIV specialist.

Monitoring fasting glucose levels every three to six months is useful in patients taking PIs because of the potential for developing glucose intolerance, insulin resistance, and type 2 diabetes. PIs can aggravate existing diabetes; patients with HIV infection who also have diabetes should be monitored closely when PIs are prescribed.[1] Diet, exercise, and weight loss are preferred over hypoglycemic drug therapy, although agents such as thiazolidinediones or metformin (Glucophage) can be considered.[1]

HEPATIC/GASTROINTESTINAL EFFECTS

Severe hepatotoxicity (i.e., more than a fivefold increase from the upper limit of normal in alanine transaminase or aspartate transaminase levels) can occur in patients treated with PIs (especially if they are taken in combination with other PIs such as saquinavir [Forto-

TABLE 1
Antiretroviral Agents Used to Treat HIV Infection

Class: NRTI	**Class: PI**
Abacavir (Ziagen)	Amprenavir (Agenerase)
Abacavir/lamivudine/zidovudine (Trizivir)	Atazanavir (Reyataz)
Didanosine (Videx)	Indinavir (Crixivan)
Emtricitabine (Emtriva)	Lopinavir/ritonavir (Kaletra)
Lamivudine (Epivir)	Nelfinavir (Viracept)
Lamivudine/zidovudine (Combivir)	Ritonavir (Norvir)
Stavudine (Zerit)	Saquinavir (Fortovase)*
Zalcitabine (Hivid)	Saquinavir mesylate (Invirase)*
Zidovudine (Retrovir)	**Class: FI**
Class: NtRTI	Enfuvirtide (Fuzeon)
Tenofovir (Viread)	
Class: NNRTI	
Delavirdine (Rescriptor)	
Efavirenz (Sustiva)	
Nevirapine (Viramune)	

HIV = human immunodeficiency virus; NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; FI = fusion inhibitor.

**—Saquinavir and saquinavir mesylate are not bioequivalent and are not interchangeable.*

vase] and ritonavir) and some NRTIs and NNRTIs such as nevirapine (Viramune) and zalcitabine (Hivid).[1,18] Co-infection with hepatitis C virus is a major risk factor for developing hepatotoxicity after initiation of PI therapy.[19,20]

Lactic acidosis has been associated with NRTI and NNRTI use; although uncommon, it has a high mortality rate.[21,22] Patients taking NRTIs may present with nonspecific gastrointestinal symptoms, diarrhea, and anorexia, with or without abnormal test results such as elevated levels of hepatic transaminases and serum lactate.[23-25] Conversely, liver-function

TABLE 2
Properties of Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

Drug	*Black box warnings**	*Adverse effects*	*Medications to avoid†*	*Food requirements*
Abacavir (Ziagen)[7]	Hypersensitivity reactions, lactic acidosis, and severe hepatomegaly with steatosis have been reported.	Fever, rash, nausea, vomiting, diarrhea, malaise, fatigue, loss of appetite, respiratory symptoms, lactic acidosis, headache, insomnia	None listed	Take without regard to meals. Coadministration with ethanol increases drug levels by 41% but has no effect on ethanol.
Didanosine (Videx)[7]	Pancreatitis, lactic acidosis, and severe hepatomegaly with steatosis have been reported.	Peripheral neuropathy, nausea, rash, pancreatitis, diarrhea, headache, fever	None listed	Take 30 minutes before or 2 hours after meals. Alcohol use increases risk of pancreatitis.
Emtricitabine (Emtriva)[8]	Lactic acidosis and severe hepatomegaly with steatosis have been reported.	Headache, diarrhea, nausea, rash, skin discoloration	None listed	Take without regard to meals.
Lamivudine (Epivir)[7]	Lactic acidosis and severe hepatomegaly with steatosis have been reported.	Minimal toxicity	None listed	Take without regard to meals.
Stavudine (Zerit)[7]	Pancreatitis, lactic acidosis, and severe hepatomegaly with steatosis have been reported.	Headache, diarrhea, rash, nausea, vomiting, pancreatitis, peripheral neuropathy, and ascending neuromuscular weakness	None listed	Take without regard to meals.
Tenofovir (Viread)[7]	Lactic acidosis and severe hepatomegaly with steatosis have been reported.	Asthenia, headache, diarrhea, nausea, vomiting, flatulence, and anorexia	None listed	Better if taken with food but not required
Zalcitabine (Hivid)[7]	Severe peripheral neuropathy, pancreatitis, lactic acidosis, severe hepatomegaly with steatosis, and hepatic failure and death in patients with possible underlying hepatitis B infection have been reported.	Peripheral neuropathy, fatigue, headache, fever, vomiting, nausea, diarrhea, rash, abnormal hepatic function, and stomatitis	None listed	Take without regard to meals.
Zidovudine (Retrovir)[7]	Hematologic toxicity, lactic acidosis, severe hepatomegaly with steatosis, and symptomatic myopathy have been reported.	Bone marrow suppression; anemia or neutropenia; gastrointestinal intolerance; headache, insomnia, asthenia, and anorexia	None listed	Take without regard to meals.

**—Severe adverse effects that have been associated with serious injury or death.*
†—See Physicians' Desk Reference for more complete information on drug interactions and contraindications.

Information from references 7 and 8.

test results and lactate levels may be elevated in asymptomatic patients.[23,24]

The prodromal stage of lactic acidosis may include unexplained onset and persistence of abdominal distention and pain, nausea, vomiting, diarrhea, anorexia, dyspnea, generalized weakness, ascending neuromuscular weakness, myalgias, paresthesias, weight loss, and hepatomegaly.[26] Laboratory evaluation may reveal hyperlactacidemia and an increased anion gap and creatine kinase, lactate dehydrogenase, C-reactive protein, lipase, and amylase levels.[1,7,25,27] Computed tomography or ultrasonography may reveal an enlarged, fatty liver.

Other risk factors for lactic acidosis include female gender, obesity, and prolonged use of NRTIs. Pregnant women taking stavudine (Zerit) or didanosine (Videx) may be at especially high risk,[1] although some cases of lactic acidosis have occurred in patients without any known risk factors.[24-26] Early recognition of lactic acidosis is vital so that the NRTI therapy can be stopped.[1,7]

DERMATOLOGIC EFFECTS

The HIV virus itself, co-infections (e.g., syphilis), infestations, and drug reactions can cause rashes in HIV-infected patients. Some HIV-associated dermatoses, including viral exanthem, herpes zoster, early molluscum contagiosum, seborrheic dermatitis, eosinophilic folliculitis, and "itchy red bump" disease, can be difficult to distinguish from drug-related effects.

Rashes can be mild and self-limiting or life-threatening, such as a hypersensitivity reaction to abacavir (Ziagen). Skin rashes occur

TABLE 3
Properties of Nonnucleoside Reverse Transcriptase Inhibitors

Drug	*Black box warnings**	*Adverse effects*
Delavirdine (Rescriptor)	None	Rash, increased transaminase levels, headache
Efavirenz (Sustiva)	None	Rash, central nervous system symptoms, psychiatric symptoms, increased transaminase levels, hepatotoxicity, false-positive results from cannabinoid tests; teratogenic in monkeys
Nevirapine (Viramune)	Severe hepatotoxicity including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure; skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions have been reported. Patients should be monitored intensively during the first 12 weeks of therapy for hepatotoxicity or skin reactions; a 14-day lead-in period must be followed strictly. Nevirapine should not be restarted after severe hepatic, skin, or hypersensitivity reactions.	Rash and hepatitis, including hepatic necrosis

**—Severe adverse effects that have been associated with serious injury or death.*
†—See Physicians' Desk Reference for more complete information about drug interactions and contraindications.

Information from reference 7.

most commonly with the use of NNRTIs[1]; they are more frequent and severe when associated with nevirapine therapy.[27] In one study,[27] 15 of 18 patients taking nevirapine had serious cutaneous manifestations such as Stevens-Johnson syndrome and toxic epidermal necrolysis. The mean time from the start of nevirapine therapy to the onset of rash was 11 days, with two thirds of the cases occurring during the first two weeks of therapy. Compared with men, women had a nearly sevenfold higher risk for developing grade 3 or 4 skin rashes.[28,29]

A two-week lead-in dose escalation schedule reduces the incidence of rash in patients who are starting nevirapine therapy.[30] Prophylactic use of systemic corticosteroids or antihistamines has not been proved uniformly effective.[29,30] However, some experts recommend antihistamine therapy for mild to moderate hypersensitivity reactions.[1] Switching to a different NNRTI in patients with a history of mild to moderate drug-associated skin rash is not recommended by most experts and should be done only with close follow-up.[1,7,30] [Reference 1—Evidence level C, consensus/expert guidelines]

Among the NRTIs and PIs, abacavir and amprenavir (Agenerase) are associated most frequently with skin rash.[1,7,30] Abacavir can cause a severe hypersensitivity syndrome with rash, fever, malaise, and gastrointestinal symptoms. Respiratory manifestations such as pharyngitis, cough, and dyspnea also may occur but are less common.[1,30,31] Patients who become sensitized to abacavir risk hypotension and a life-threatening reaction if they try to use it again. Cases of abacavir hypersensi-

Medications to avoid†	*Food requirements*	*Miscellaneous*
Dihydroergotamine mesylate (DHE 45), ergotamine (Ergostat), H_2-receptor antagonists, lovastatin (Mevacor), midazolam (Versed), proton pump inhibitors, rifabutin (Mycobutin), rifampin (Rifadin), simvastatin (Zocor), triazolam (Halcion), St. John's wort	Take without regard to meals.	May increase levels of dapsone, warfarin (Coumadin), and quinidine. May increase levels of sildenafil (Viagra) and adverse effects; do not exceed 25 mg in a 48-hour period.
Dihydroergotamine mesylate, ergotamine, midazolam, triazolam, St. John's wort	Take before or after meals; high-fat/high-calorie meals increase peak plasma concentrations of capsules by 39% and tablets by 79%.	Increases levels of ethinyl estradiol by 37%; use alternate method of contraception.
St. John's wort	Take without regard to meals.	May decrease levels of ethinyl estradiol by approximately 20%; use alternate method of contraception.

TABLE 4
Properties of Protease and Fusion Inhibitors

Drug	*Black box warnings**	*Adverse effects*
Amprenavir (Agenerase)[7]	Because of potential risk for toxicity from substantial amounts of the excipient propylene glycol, the oral solution is contraindicated in pregnant women, children younger than 4 years, patients with hepatic or renal failure, and patients treated with disulfiram (Antabuse) or metronidazole (Flagyl). The oral solution should be used only when capsules or other PIs cannot be used.	Gastrointestinal intolerance, rash, oral paresthesias, transaminase elevation, hyperglycemia, fat redistribution, and lipid abnormalities. May increase bleeding episodes in patients with hemophilia.
Atazanavir (Reyataz)[9]	None	Nausea, jaundice, arrhythmia, hyperglycemia, fat redistribution. May increase bleeding episodes in patients with hemophilia.
Enfuvirtide (Fuzeon)[10,11]	None	Injection site reactions, hypersensitivity reactions, eosinophilia. In clinical trials, rate of bacterial pneumonia increased in treated patients.
Indinavir (Crixivan)[7]	None	Nephrolithiasis, gastrointestinal intolerance and nausea, increased indirect bilirubinemia, transaminase elevation, headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, hyperglycemia, hemolytic anemia, fat redistribution, and lipid abnormalities. May increase bleeding episodes in patients with hemophilia.
Lopinavir/ ritonavir (Kaletra)[7]	None	Gastrointestinal intolerance, asthenia, elevated transaminase enzymes, hyperglycemia, fat redistribution, and lipid abnormalities. May increase bleeding episodes in patients with hemophilia.
Nelfinavir (Viracept)[7]	None	Diarrhea, hyperglycemia, transaminase elevation, fat redistribution, and lipid abnormalities. May increase bleeding episodes in patients with hemophilia.
Ritonavir (Norvir)[7]	Coadministration with certain nonsedating antihistamines, sedative hypnotics, antiarrhythmics, or ergot alkaloid preparations can result in potentially serious or life-threatening adverse events.	Gastrointestinal intolerance, paresthesias (circumoral and extremities), hepatitis, pancreatitis, asthenia, taste perversion, >200% increase in triglyceride level, elevated creatine kinase and uric acid levels, hyperglycemia, fat distribution, and lipid abnormalities. May increase bleeding episodes in patients with hemophilia.

Medications to avoid†	*Food requirements*	*Miscellaneous*
Bepridil (Vascor), dihydroergotamine mesylate (DHE 45), ergotamine (Ergostat), lovastatin (Mevacor), midazolam (Versed), rifampin (Rifadin), simvastatin (Zocor), triazolam (Halcion), St. John's wort, garlic supplements	Can be taken with or without food but not with high-fat meals (fat decreases blood concentration).	Store at room temperature. May increase levels of sildenafil (Viagra); do not exceed 25 mg in a 48-hour period.
Bepridil, cisapride (Propulsid), ergotamine, indinavir (Crixivan), lovastatin, midazolam, pimozide (Orap), rifampin, simvastatin, triazolam, St. John's wort, garlic supplements	Take with food.	Store at room temperature.
None	None (injection)	None
Dihydroergotamine mesylate, ergotamine, lovastatin, midazolam, rifampin, simvastatin, triazolam, St. John's wort, garlic supplements	Take 1 hour before or 2 hours after meals. Can take with skim milk or a low-fat meal. Recommended water intake is at least 1.4 L (48 fl oz) per day.	Store at room temperature. Carbamazepine (Tegretol) substantially decreases blood levels; consider alternative agent. Grapefruit juice decreases blood levels by 26%. Increases levels of sildenafil by 340%; do not exceed 25 mg in a 48-hour period.
Dihydroergotamine mesylate, ergotamine, flecainide (Tambocor), lovastatin, pimozide, propafenone (Rythmol), rifampin, simvastatin, triazolam, St. John's wort, garlic supplements	Take with food; a moderate-fat meal increases blood concentration of capsules and solution by 48% and 80%, respectively. Recommended water intake is 2 to 3 L (68 to 101 fl oz) per day.	Oral solution contains 42% alcohol. Refrigerated capsules are stable until expiration date; capsules can be stored at room temperature for 2 months. Decreases levels of ethinyl estradiol by 42%; use alternate method of contraception. May increase levels of sildenafil; do not exceed 25 mg in a 48-hour period.
Dihydroergotamine mesylate, ergotamine, lovastatin, midazolam, rifampin, simvastatin, triazolam, St. John's wort, garlic supplements	Take with a meal or snack.	Store at room temperature. Decreases norethindrone (Norlutin) levels by 18% and ethinyl estradiol levels by 47%; use alternate method of contraception. Increases atorvastatin (Lipitor) levels by 74%; use with caution. May increase sildenafil levels; do not exceed 25 mg in a 48-hour period.
Amiodarone (Cordarone), bepridil, dihydroergotamine mesylate, ergotamine, flecainide, lovastatin, midazolam, pimozide, propafenone, quinidine, simvastatin, triazolam, St. John's wort, garlic supplements	Take with food, if possible, to improve tolerability.	Refrigerate capsules; capsules can be stored at room temperature for up to 30 days. Oral solution should not be refrigerated. Increases clarithromycin (Biaxin) levels by 77%. Adjust dosage in patients with renal insufficiency. Decreases ethinyl estradiol levels by 40%; use alternate method of contraception. Carbamazepine toxicity has been reported after introduction; use with caution and monitor anticonvulsant level closely. Increases desipramine (Norpramin) level by 145%; reduce dosage. Decreases theophylline level by 47%; monitor level. Doubles sildenafil level; do not exceed 25 mg in a 48-hour period.

Table 4 continued on next page

TABLE 4 *(continued)*

Drug	*Black box warnings**	*Adverse effects*
Saquinavir (Fortovase)[7]	None	Gastrointestinal intolerance, dyspepsia, headache, elevated transaminase level, hyperglycemia, fat redistribution, and lipid abnormalities. May increase bleeding episodes in patients with hemophilia.
Saquinavir mesylate (Invirase)[7]	Saquinavir and saquinavir mesylate are not bioequivalent and cannot be used interchangeably.	Gastrointestinal intolerance, headache, elevated transaminase level, hyperglycemia, fat redistribution, and lipid abnormalities. May increase bleeding episodes in patients with hemophilia.

PI = protease inhibitor.

**—Severe adverse effects that have been associated with serious injury or death.*
†*—See Physicians' Desk Reference for more complete information about drug interactions and contraindications.*

Information from references 7 and 9 through 11.

tivity syndrome should be reported to the Abacavir Hypersensitivity Registry (telephone: 800-270-0425).

ORTHOPEDIC EFFECTS

Avascular necrosis and decreased bone density have been reported in patients with HIV infection.[30,32,33] Avascular necrosis may not be associated with a specific antiretroviral regimen, but it has been linked to corticosteroid use in some patients.[33,34] Other factors associated with osteonecrosis include alcohol abuse, hemoglobinopathies, hyperlipidemia, and previous use of antihyperlipidemics.[33] One prospective study[33] found that no single test or combination of tests, including physical examination and plain-film radiography, was predictive of osteonecrosis. However, at the time of magnetic resonance imaging, patients with osteonecrosis also were found to have significantly higher viral loads and platelet counts, and 93 percent had positive anticardiolipin antibodies.[33]

Studies of bone demineralization in a limited number of patients taking antiretroviral therapy have shown that up to 50 percent of patients on a PI-based regimen developed evidence of osteopenia compared with 20 percent of untreated patients and patients on a non-PI-based regimen.[35] Other studies have shown that patients with lipodystrophy and extensive prior PI use had osteopenia (28 percent) or osteoporosis (9 percent).[30]

Rashes in patients with HIV infection or AIDS can be caused by the virus itself, co-infections, infestations, or drug reactions.

Interactions

DRUG-FOOD INTERACTIONS

If antiretroviral drugs are not taken correctly with respect to meals and other medications, a reduction of as much as 80 percent in bioavailability is possible.[7,30] Fortunately, an increasing number of antiretroviral drugs have no specific food requirements *(Tables 2 through 4)*.[7-11]

A full meal can reduce serum concentration of indinavir (Crixivan) by up to 80 percent; unlike other PIs such as saquinavir, nelfinavir (Viracept), and ritonavir, this agent should be

Medications to avoid†	*Food requirements*	*Miscellaneous*
Dihydroergotamine mesylate, ergotamine, lovastatin, midazolam, rifampin, simvastatin, triazolam, St. John's wort, garlic supplements	Take with a large meal.	Refrigerate or store at room temperature for up to 3 months.
Dihydroergotamine mesylate, ergotamine, lovastatin, midazolam, rifampin, simvastatin, triazolam, St. John's wort, garlic supplements	When taken with ritonavir, timing of meals has no effect.	Store at room temperature. Grapefruit juice increases blood level. Increases sildenafil level 2- to 11-fold; use a 25-mg starter dose of sildenafil.

taken on an empty stomach. Conversely, meals reduce the gastrointestinal side effects and increase the absorption of ritonavir and saquinavir.

Patients taking indinavir or lopinavir/ritonavir (Kaletra) should drink 150 mL (5.1 oz) of water per hour for three hours after each dose. Indinavir can cause interstitial nephritis and renal calcinosis; patients taking this drug should drink at least 1.5 L (50.7 oz) of water per day.

DRUG-DRUG INTERACTIONS

Drug-drug interactions are more common and potentially more severe with PIs than other classes of antiretroviral agents. Many of the drug interactions involving these agents can cause life-threatening reactions or reduced bioavailability of the PI. Even a short exposure to suboptimal levels of antiretroviral agents can lead to irreversible viral resistance and loss of clinical benefit (especially among drugs with a low barrier to resistance, such as lamivudine [Epivir] and NNRTIs). Therefore, knowledge of both types of interaction is extremely important.[1,7,30]

Because they stimulate the cytochrome P450 system, drugs such as phenytoin (Dilantin), rifampin (Rifadin), carbamazepine (Tegretol), phenobarbital, and dexamethasone—and even grapefruit juice—can cause a clinically significant increase in PI metabolism that can reduce serum drug concentrations.[21,30] By inhibiting the same isoform of the cytochrome P450 system that breaks down certain drugs, PIs—especially ritonavir—can increase serum levels of many drugs that are commonly prescribed in primary care.[1,7,30] These drugs should be avoided or used cautiously in patients with HIV infection.

Because they stimulate hepatic glucuronides, PIs can reduce serum concentrations of glucuronated drugs such as codeine and morphine.[1,7,30]

Ritonavir can decrease serum levels of

If antiretroviral drugs are not taken correctly with respect to meals and other drugs, a reduction of as much as 80 percent in bioavailability is possible.

ethinyl estradiol, sulfamethoxazole/trimethoprim (Bactrim, Septra), and zidovudine (Retrovir, formerly called azidothymidine [AZT]) to the point of clinical failure.[30,36] Providers should check product labels for the extensive listing of drug interactions before prescribing additional medications to patients who are taking PIs.

DRUG-HERB INTERACTIONS

In recent years, herbal medicine has grown faster than any other alternative treatment in the United States.[37] However, many patients may not consider herbal remedies to be "medicine" and might not think of telling their physicians that they are taking them.[38]

Garlic is the third leading herbal product in the United States, with total annual retail sales of $84 million.[37] Its reputation as a natural cholesterol fighter has made it popular among patients taking medications, such as PIs, that can increase lipid levels. However, garlic supplements have been shown to dramatically reduce serum concentrations of saquinavir by as much as 50 percent; levels remained lowered even after the patient stopped taking garlic.[39]

St. John's wort can influence serum levels of PIs and NNRTIs.[40,41] By stimulating cytochrome P450 activity, it can lower serum concentration of indinavir by up to 80 percent.[42]

TABLE 5
Tips for Improving Adherence to Antiretroviral Regimens

Educate the patient about the goals of therapy and the importance of adherence to the regimen.
Anticipate and treat side effects.
Simplify food requirements.
Reduce dosage frequency and number of pills, if possible.
Recruit the patient's family and friends for support.
Provide a written dosing schedule, pictures of medications, daily or weekly pillboxes, alarm clocks, pagers, or other reminders.
Monitor adherence and intensify management in periods of low adherence.
Consider the impact of new diagnoses on adherence (e.g., depression, wasting, recurrent chemical dependency) and include adherence intervention in the management plan.
Use nurses, pharmacists, peer educators, volunteers, case managers, drug counselors, physician assistants, nurse practitioners, and research staff to reinforce adherence.

Information from reference 44.

Adherence to Therapy

Adherence to antiretroviral regimens is critical.[7,30] Patients must take 95 percent of their pills to achieve an 80 percent likelihood of HIV suppression below 50 copies per mL. With less than 95 percent adherence, the probability of suppression to undetectable levels drops to less than 50 percent.[43]

Patients must be committed to and capable of adhering to complicated regimens with high pill burdens; some regimens require more than 20 pills per day. Compared with other PI regimens, indinavir and lopinavir/ritonavir require the fewest number of capsules per day.

To familiarize patients with the rigors of antiretroviral therapy, some centers offer "dry runs" with jellybeans before patients start their first regimen. This exercise has not been proved to improve adherence.

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Failure to take medications regularly and reliably causes the virus to be exposed to suboptimal drug serum concentrations and drastically increases the chance that drug resistance will develop. The patient's relationship with the physician has been shown to be one of the greatest determinants of adherence.[43] Even in highly committed patients, adherence wanes over time. A phenomenon described as "pill fatigue" or "treatment fatigue" can occur.[1,7,30] Monitoring adherence at every clinical encounter is essential. Reasonable responses to decreasing adherence include increasing the intensity of clinical follow-up, shortening the follow-up interval, and recruiting additional health team members, depending on the nature of the problem *(Table 5)*.[44]

Depression has been reported in more than one half of HIV-infected patients and in up to 60 percent of HIV-infected women.[4] Cessation of all medications at the same time may be more desirable than uncertain adherence during a short exacerbation of chronic depression.

The opinions and assertions contained herein are the views of the authors and are not to be construed as official or as reflecting the views of the U.S. Army Medical Department or the U.S. Army at large.

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