



Pharmacy

How common illicit substances interact with antiretroviral agents

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Recent reports in the literature have brought more attention to the life-threatening interactions, including deaths, that have occurred when protease inhibitors were combined with illicit drugs such as ecstasy (MDMA) and GHB (gamma-hydroxybutyrate) (Harrington 1999).

Although protease inhibitors have dramatically improved the prognosis for many HIV-infected patients, they are associated with numerous adverse effects including increases in serum glucose, triglycerides, lipodystrophy, hepatitis, nephrolithiasis and a large variety of GI side effects (Flexner, 1998).

In addition, protease inhibitors can cause serious adverse reactions and interactions when administered in combination with other substances, including illicit drugs, whose metabolism may be altered as a result of the inhibitory effects of the PIs on the cytochrome P450 enzyme system.

Illicit substances most commonly abused include cocaine, marijuana, methamphetamine, ecstasy, heroin, methadone, ketamine, crystal and GHB.

As a result of the myriads of side effects that could follow use of these substances (see listing of side effects for ecstasy on following page), combination of

these substances with protease inhibitors especially increases the likelihood of an overdose due to these agents, for example, ecstasy.

Cocaine has been reported to increase the speed at which HIV replicates while combination of the protease inhibitors with marijuana increases levels of tetrahydrocannabinoids in the blood.

Because combination of methamphetamine with ritonavir (Norvir) causes an increase in the potency of ritonavir, two to three fold, the likelihood of overdose with methamphetamine is increased.

Concomitant use of ketamine in the presence of the protease inhibitors causes hepatitis, while ritonavir decreases plasma levels of heroin by 50%.

Potency of methadone is decreased in the presence of ritonavir, indinavir (Crixivan) and nevirapine (Viramune), while methadone increases the potency of ritonavir by 50%.

Nevirapine was demonstrated to reduce plasma methadone levels and to precipitate opiate withdrawal in patients who were maintained on methadone for narcotics addiction (Altice, 1999).

More recent studies have reported decreases in the amount of stavudine (Zerit) and didanosine (Videx) absorbed from the digestive tract into the bloodstream in the presence of methadone.

Table 1 gives the highlights of most of the side effects that

may be exacerbated by the use of ecstasy or MDMA, a powerful street drug recently associated with fatal drug interactions when co-administered with ritonavir.

Drug interactions between opioid analgesics and protease-inhibitor antiretroviral agents

Since most opiates are substrates of the CYP450 enzyme system, when they are coadministered with cytochrome P450 enzyme inhibitors such as the protease inhibitors, erythromycin and clarithromycin, marked increases in serum levels can occur, patients should be monitored for oversedation and initial dosages should be decreased by 50%.

Patients abusing opiate drugs are at risk of toxicity when co-administered with these agents and should be counseled appropriately (Maurer et al. 1993).

Table II lists metabolic pathways of frequently abused drugs potentially affected by co-administration with the protease inhibitors. ❖

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Table 1: Side effects of Ecstasy (MDMA) that may be exacerbated when used along with conventional drugs with similar side effects

Bradycardia	Pruritus
Faintness	Rash
Euphoria	Decreased libido
Dysphoria	Nausea and vomiting
Headache	Urinary retention
Insomnia	Visual disturbances
Drowsiness	Respiratory depression
Physical and psychological dependence	

Source: Centers for Disease Control and Prevention. Multistate outbreak of poisonings associated with illicit use of gamma hydroxybutyrate use-New York and Texas, 1995-1996. MMWR Morb Mort Wkly Rep. 1997; 46:28283.

Table 2: Metabolic pathways of frequently abused drugs potentially affected by human immunodeficiency virus-1 protease inhibitors (adapted from Harrington, 1999)

FREQUENTLY ABUSED DRUG	Metabolic Pathway Used (P450 Isoenzyme)
Opiates	
Methadone, Alfentanil, Fentanyl Meperidine Codeine, hydrocodone, oxycodone Heroin, Morphine, hydromorphone Propoxyphene (Darvon)	Cytochrome P450 (CYP3A4) Cytochrome P450 (CYP3A4?) Cytochrome P450 (CYP2D6) Glucuronidation? Cytochrome P450 (CYP2D6)
Benzodiazepines	
Diazepam (Valium) Alprazolam, clorazepate, estazolam, flurazepam, midazolam, triazolam	Cytochrome P450 (CYP3A4, CYP2C19) Cytochrome P450 (CYP3A4)
Other drugs prone to abuse	
Marijuana, dronabinol, zolpidem Sildenafil (Viagra)* Cocaine**	Cytochrome P450 (CYP3A4) Cytochrome P450 (CYP3A4) Hydrolysis by plasma cholinesterase.

*AUC of sildenafil (Viagra) is increased 2-11 fold in the presence of all protease inhibitors; patients should not exceed 25mg in any given 48 hour period.

**Cocaine increases the speed at which HIV-1 virus replicates and so worsens overall prognosis by abolishing gains made by antiretroviral therapy. Metabolism of cocaine should not be affected by protease inhibitors.

Plan ahead to attend HIV conferences...

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10th Conference on Retroviruses and Opportunistic Infections
Boston, Massachusetts
Email: info@retroconference.org

▲ March 27-30, 2003
2003 National HIV Prevention Conference
Atlanta, Georgia
Sponsor: Centers for Disease Control and Prevention (CDC)

▲ April 2003
5th International Conference on Nutrition and HIV Infection
Cannes, France
Email: hivcannes@wanadoo.fr

▲ April 27-May 1, 2003
16th International Conference on Antiviral Research
Savannah, Georgia
Email: korbabe@gusun.georgetown.edu

▲ April 28-30, 2003
7th International Conference on Malignancies in AIDS and Other Immunodeficiencies: Basic, Epidemiologic and Clinical Research
Bethesda, MD
Email: jqquinn@mail.nih.gov

▲ May 15-18, 2003
13th Annual Clinical Care Options for HIV Symposium
Scottsdale, Arizona
Email: DPeralta@contacthmc.com

▲ June 10-14, 2003
XII International HIV Drug Resistance Workshop: Basic Principles and Clinical Implications
Cabo Del Sol, Los Cabos, Mexico
Phone: (770) 946 3480

▲ July 8-11, 2003
5th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV
Paris, France
Email: lipodystrophy@us.intmedpress.com

▲ July 13-17, 2003
The 2nd IAS Conference on HIV Pathogenesis and Treatment
Paris, France
Email: ias2003@jcdconseil.com