



Topic: Opioid Therapies, HIV Disease and Drug Interactions

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Guideline coverage

TIP #40, Special Populations: Patients with Medical Comorbidities (pgs. 67-68).

Clinical questions

1. Do drug interactions of clinical significance occur between methadone or buprenorphine and HIV medications?
2. How should I determine whether an opiate-addicted patient with HIV disease should be treated with methadone or buprenorphine?

Background

Injection drug use is a risk factor for HIV infection. Many, if not most injection drug users are addicted to opiates. The treatment of choice for opioid dependence in these patients is opioid maintenance therapy available principally as either methadone or buprenorphine pharmacotherapy (Johnson et al. 2000).

Preclinical studies elucidating the clinical pharmacology of antiretroviral medications and opioids indicate that drug interactions are likely to occur (Kumar et al. 1996, Iribarne et al., 1998). Methadone and buprenorphine are primarily metabolized by hepatic cytochrome P450 enzymes (CYP 450), specifically CYP 450 3A4 (Moody et al., 1997, Iribarne et al, 1996). A number of antiretroviral medications are substrates of and have been shown in preclinical studies to inhibit the activity of CYP 450 3A4 leading to speculation of opioid toxicity and/or toxicity related to increased exposure to the HIV medications in those receiving maintenance therapies. Conversely, if an antiretroviral agent were to induce CYP 450 enzyme production, an opiate abstinence syndrome could result placing the patient at risk for relapse to illicit drug use and nonadherence to HIV medication therapies.

To date (September 2006), methadone has been associated with several clinically important, adverse drug interactions with HIV medications. Buprenorphine has been studied in combination with antiretroviral medications more recently. Table 1 summarizes drug interactions that have been identified between antiretroviral medications and either methadone or buprenorphine. The clinical importance of drug interactions lies in the associated adverse events that occur. Drug interactions that lead to reduced methadone concentrations in the blood have been associated with opiate withdrawal syndromes which themselves have been linked to non-adherence to HIV medications and to increases in illicit drug use including high risk behaviors such as injection drug use. To date, reductions in buprenorphine concentrations resulting from drug interactions have not been associated with opiate withdrawal. Drug interactions that lead to low plasma concentrations of antiretroviral medications may produce subtherapeutic concentrations that may be clinically ineffective and risk the possibility of the development of viral resistance. Similarly, toxicities resulting from drug interactions that might increase plasma concentrations of opioids or antiretroviral medications include the risk of non-adherence or sporadic adherence to HIV regimens that may result in the development of viral resistance. These consequences underscore the need for clinicians to be familiar with the drug interactions of importance between opioids and antiretroviral therapies so that they can monitor patients for adverse events and intervene as needed as well as to educate their patients.

Table 1: Identified Drug Interactions between Antiretroviral Medications and Methadone or Buprenorphine

HIV Medication	Interaction with Methadone	Interaction with Buprenorphine
Nucleoside Reverse Transcriptase Inhibitors		
Zidovudine (AZT)	↑ AZT AUC by 40%, AZT toxicity observed requiring dose adjustment in several participants, no effect on methadone levels (McCance-Katz <i>et al.</i> , 1998)	Non-clinically significant ↓ AZT concentrations (McCance-Katz <i>et al.</i> , 2001)
Didanosine (ddl) tablet	↓ ddl AUC by 63%, no effect on methadone levels (Rainey <i>et al.</i> , 2000)	Not studied
Didanosine (ddl) enteric-coated	No significant effect of methadone on ddl (Friedland <i>et al.</i> , 2002)	Under study
Zalcitabine (ddC)	None	Not studied
Lamivudine (3TC)	None	Under study
Lamivudine/zidovudine (Combivir)	None (Rainey <i>et al.</i> , 2002)	
Stavudine (d4T)	↓ d4T AUC by 25% (Rainey <i>et al.</i> , 2000)	Not studied
Abacavir (ABC)	↑ Methadone clearance, but no withdrawal, no clinically significant effect on ABC concentrations (Sellers <i>et al.</i> , 1999),	Not studied
Tenofovir	No significant interaction	Under study
Non-Nucleoside Reverse Transcriptase Inhibitors		
Nevirapine	Withdrawal symptoms, need for increased methadone dose (Altice <i>et al.</i> , 1999), 40% decrease in methadone (Stocker <i>et al.</i> 2004)	Under study
Delavirdine (DLV)	↑ Methadone levels without toxicity (McCance-Katz, <i>et al.</i> 2006), no effect on DLV	↑ BUP concentrations without toxicity, no effect on DLV (McCance-Katz <i>et al.</i> in press)
Efavirenz (EFV)	↓ Methadone levels, withdrawal symptoms, ↑ methadone dose necessary (Clarke <i>et al.</i> , 2001, McCance-Katz <i>et al.</i> 2002)	↓ BUP levels, no withdrawal, no dose change needed, no effect on EFV levels (McCance-Katz, <i>et al.</i> in press)
Protease Inhibitors		
Nelfinavir (NLF)	↓ Methadone levels, but no withdrawal symptoms observed (McCance-Katz <i>et al.</i> , 2004), increased NLF, decreased M8 metabolite, no clinically significant change in NLF	No effect on BUP (McCance-Katz <i>et al.</i> in press), no significant effect of BUP on NLF
Indinavir	Not studied	Not studied
Ritonavir (RTV)	↑ Methadone levels reported, not clinically significant (McCance-Katz <i>et al.</i> 2003)	↑ BUP levels, not clinically significant, no effect of BUP on RTV
Saquinavir	↓ Methadone levels (S entantiomer), no withdrawal (Gerber <i>et al.</i> 2002)	Not studied
Amprenavir	↓ methadone, no withdrawal	Not studied
Lopinavir/ritonavir (L/R)	↓ methadone, withdrawal may occur, methadone may need to be increased (McCance-Katz <i>et al.</i> , 2003)	No significant effect on BUP, no effect of BUP on L/R (McCance-Katz, in press)
Atazanavir (ATZ) or Atazanavir/ritonavir (ATV/r)	No effect of ATZ on methadone, no effect of methadone on ATZ (Friedland <i>et al.</i> , 2005)	Significant increase in BUP and norbuprenorphine; sedation may occur (McCance-Katz <i>et al.</i> , under review); clinical observation of sedation and cognitive impairment with ATV/r (Bruce, 2005)

Patient education

When a patient with HIV disease is seeking pharmacotherapy for opioid dependence, they should be informed of the risks and benefits of methadone or buprenorphine therapy including the possibility of adverse drug interactions that might be associated with either symptoms of opiate withdrawal (to date this has only been observed with certain antiretroviral medications and methadone) or opiate excess (this has been recently observed in several patients receiving the protease inhibitor combination atazanavir/ritonavir and buprenorphine). Buprenorphine appears to have fewer adverse drug interactions with HIV medications than does methadone. Buprenorphine treatment may also be preferable to methadone for many patients in that physicians with appropriate training and qualifications can prescribe buprenorphine for opioid addiction; thus one physician may be able to provide both HIV care and treatment for opioid dependence. Demonstration projects of this model of care are currently underway (see www.bhives.org).

Recommendations

Level of evidence: **High – Clinical observation and controlled pharmacokinetics/pharmacodynamics studies**

- 1. For the patient with HIV disease who is methadone-maintained and requires initiation of highly active antiretroviral therapy (HAART):** Patients should continue on their current methadone dose and should be informed of the potential for drug interactions that may cause them to experience either symptoms of opiate withdrawal, opiate excess (sleepiness, impaired thinking), or symptoms of antiretroviral toxicity (such symptoms are specific to the medications being prescribed and should be discussed with the patient; thus far the only antiretroviral medication that has been associated with toxicity is zidovudine (AZT) and this appears to be a rare event). Patients should be encouraged to immediately report any adverse symptoms to their HIV treatment provider and to clinical staff at the methadone maintenance program. It should be recognized that patients receiving HAART and methadone may require methadone dose adjustments. A trough methadone level prior to initiation of HAART and when a patient experiences symptoms thought to be opiate withdrawal/excess may be helpful. A significant decrease or increase in trough methadone concentration with antiretroviral treatment would indicate a need for increasing/decreasing the methadone dose. In patients experiencing acute, severe symptoms; the methadone dose should be addressed immediately. It may be helpful to obtain a trough methadone level, but in such cases, the dose of methadone should be immediately addressed in an attempt to prevent non-adherence to HIV medications and/or abuse of illicit drugs.
- 2. For the patient with HIV disease who is buprenorphine-maintained and requires initiation of highly active antiretroviral therapy (HAART):** Patients should continue on their current buprenorphine/naloxone dose. Patients should be informed of the potential for drug interactions with HIV medicines that may cause them to experience symptoms of opiate excess (sleepiness, impaired thinking) (this has been observed only with atazanavir/ritonavir to date) or potentially, opiate abstinence (this has not been observed between buprenorphine and any antiretroviral medication studied to date). Patients should be encouraged to report any adverse events experienced which should be clinically evaluated and if necessary, buprenorphine dose adjustment should be made.
- 3. For the opiate-addicted patient with HIV disease considering opioid therapy:** The choice of opioid therapy should be based on the assessment of patient clinical needs. For example, patients with high amounts of daily opiate use, those who have a history of high-dose methadone maintenance treatment (> 80 mg daily), those with chronic pain conditions that may require opioid therapy, pregnant women (at this time methadone maintenance remains the standard of care for pregnant, opiate-addicted patients), and those who may benefit from the increased structure of the methadone maintenance program may be better suited to methadone treatment. Those with HIV physicians who

can provide buprenorphine treatment may be best treated by that physician for both disorders. Patients needing HAART may benefit from a trial of buprenorphine treatment due to the reduced likelihood of adverse drug interactions as compared to methadone. Any patient treated with HAART and initiating opioid therapy warrants clinical observation to determine whether adverse interactions occur and, if so, how to address these interactions.

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PCSS Guidances use the following levels of evidence*:

- **High** = Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate** = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low** = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.\
- **Very low** = Any estimate of effect is very uncertain.

Type of evidence:

- Randomized trial = **high**
- Observational study = **low**
- Any other evidence = **very low**

* Grading quality of evidence and strength of recommendations
British Medical Journal, 2004; 328; 1490-