

**Opioid Pain
and
Addiction
Management
Medications -
Drug
Interactions with
HIV Antiretrovirals**

A Drug
Interaction
Guide for
Clinicians

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OpioiD Pain and Addiction Management Medications - Drug Interactions with HIV Antiretrovirals: A Drug Interaction Guide for Clinicians

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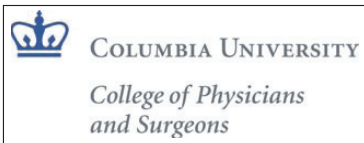
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Disclaimer:

The data in this guide are intended for use by clinicians and other health care providers as guidance to minimize drug interactions and toxicities among patients being treated with pain management / addiction management medications in conjunction with antiretrovirals. These guidelines are for informational purposes only and cannot identify medical risks specific to an individual patient or recommend patient treatment. The absence of typographical errors is not guaranteed. These guidelines are not necessarily all-inclusive. Use of these guidelines indicates acknowledgement that neither NY/NJ AETC, nor the authors will be responsible for any loss or injury, sustained in connection with, or as a result of, the use of these guidelines. Users of this guide should consult other sources before prescribing medications or treatment. Data were compiled from published studies and anecdotal reports as of Winter 2010.



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Opioid Pain and Addiction Management Medications - Drug Interactions with HIV Antiretrovirals

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		
Generic Name	Brand Name	Route of Elimination/Metabolism
Delavirdine, DLV	Rescriptor®	CYP 3A4 inhibitor
Efavirenz, EFV	Sustiva®	CYP 3A4 inducer and inhibitor
Nevirapine, NVP	Viramune®	CYP 3A4 inducer
Etravirine, ETV	Intence™	CYP 3A4 inducer, inhibitor of 2C9, 2C19

NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS		
Generic Name	Brand Name	Route of Elimination/Metabolism
Abacavir, ABC	Ziagen®	Metabolized by alcohol dehydrogenase and glucuronyl transferase
Didanosine, ddl	Videx EC®	Renal excretion 50%
Emtricitabine, FTC	Emtriva®	Renal
Lamivudine, 3TC	Epivir®	Renal
Stavudine, d4T	Zerit®	Renal excretion 50%
Tenofovir, TDF	Viread®	Renal
Zidovudine, AZT	Retrovir®	Metabolized to AZT glucuronide, renal excretion

COMBINATION REVERSE TRANSCRIPTASE INHIBITORS		
Generic Name	Brand Name	Route of Elimination/Metabolism
Abacavir and lamivudine	Epzicom®	See individual medications
Abacavir, zidovudine, and lamivudine	Trizivir®	See individual medications
Efavirenz, tenofovir, emtricitabine	Atripla®	See individual medications
Tenofovir and emtricitabine	Truvada®	See individual medications
Zidovudine and lamivudine	Combivir®	See individual medications

Opioid Pain and Addiction Management Medications - Drug Interactions with HIV Antiretrovirals

<u>PROTEASE INHIBITORS</u>		
Generic Name	Brand Name	Route of Elimination/Metabolism
Atazanavir, ATV	Reyataz®	CYP 3A4 inhibitor and substrate
Darunavir, DRV	Prezista®	CYP 3A4 inhibitor and substrate
Fosamprenavir, FPV	Lexiva®	CYP 3A4 inhibitor, inducer and substrate
Indinavir, IDV	Crixivan®	CYP 3A4 inhibitor
Lopinavir/ritonavir, LPV/r	Kaletra®	CYP 3A4 inhibitor and substrate
Nelfinavir, NFV	Viracept®	CYP 3A4 inhibitor and substrate
Ritonavir, RTV	Norvir®	CYP 3A4 and 2D6 inhibitor
Saquinavir, SQV	Invirase®	CYP 3A4 inhibitor and substrate
Tipranavir, TPV	Aptivus®	CYP 3A4 and 2D6 inhibitor

<u>FUSION INHIBITOR</u>		
Generic Name	Brand Name	Route of Elimination/Metabolism
Enfuvirtide, ENF	Fuzeon®	Catabolism to amino acids

<u>CCR5 INHIBITOR</u>		
Generic Name	Brand Name	Route of Elimination/Metabolism
Maraviroc, MRV	Selzentry®	CYP 3A4 substrate

<u>INTEGRASE INHIBITOR</u>		
Generic Name	Brand Name	Route of Elimination/Metabolism
Raltegravir	Isentress®	Metabolized by glucuronidation, not CYP 450

Contraindications, Warnings, Precautions and Adverse Events

Select Contraindications, Warnings, Precautions, and Adverse Reactions are included for medications used for pain management, opioid dependence, and alcohol dependence.

NOTE: Not all contraindications, warnings and precautions for all medications included in this guide are listed. Please refer to product labeling for each specific medication for additional information.

Select Contraindications Specific to Opioids

All opioid analgesics should be considered contraindicated in patients with respiratory depression, severe bronchial asthma, during acute asthma exacerbations, severe CNS depression or in patients with prior hypersensitivity to the specific drug or any components of the products. Use caution in patients receiving other CNS depressants. Narcotics may also obscure the clinical course for patients with head injuries.

Fentanyl - Transdermal fentanyl should not be used for short term pain management or for as needed pain management. Initial doses should not exceed 25mcg/hr at initiation of opioid therapy.

Meperidine, morphine - Do not use in patients receiving monoamine oxidase inhibitors (MAOIs) or in those who have received them in the past 14 days.

Select Warnings, Precautions and Adverse Reactions Specific to Opioids

SPECIAL COMMENT ABOUT CONTROLLED RELEASE FORMULATIONS

Controlled release products - Controlled release products should always be used with caution due to the large amounts of medication included in the formulations.

Contraindications, Warnings, Precautions and Adverse Events

Controlled release morphine and oxycodone (ie: MS Contin, Oxycontin) tablet formulations should not be crushed. Crushing, chewing, snorting or injecting contents of controlled release tablets can result in overdose or death.

Controlled release fentanyl transdermal may continue to be absorbed from the skin for 17 or more hours after patch removal; monitor patients for extended time period in patients experiencing respiratory or CNS depression associated with transdermal fentanyl. Fever has been reported to increase transdermal fentanyl absorption due to increased skin permeability. Similar fentanyl increases with the transdermal system have been reported with heating pads, electric blankets, saunas and hot tubs.

Other Warnings, Precautions and Adverse Reactions

Allergic and Cutaneous Reactions - Allergic reactions can occur with the use of opioid analgesics which may require discontinuation. Allergic reactions may include but are not limited to rash, hives and more severe skin reactions. Cross allergenicity may occur with use of other opioid analgesics. Severe anaphylactic reactions may also occur that can include hypotension, respiratory depression, and shock.

Bradycardia - Bradycardia may occur with opioid analgesics, especially with fentanyl. Use caution in patients with known bradyarrhythmias.

CNS depression - Dizziness, excess sedation and euphoria may occur with opioid analgesics. Use caution when using opioid analgesics in patients receiving other CNS depressants. This includes many psychotropic medications in the drug classes of antipsychotics, antidepressants, anxiolytics and sedative-hypnotics, as well as other CNS depressants including alcohol. In patients with renal or hepatic dysfunction, the active metabolite of meperidine (normeperidine) may accumulate and cause increased CNS adverse reactions. Avoid in patients with renal or hepatic impairment. CNS depression can be reversed with opioid antagonists such as naloxone.

Gastrointestinal - Nausea, vomiting and constipation can occur in patients receiving opioid analgesics. Consider use of stool softeners or laxatives when initiating narcotics to prevent constipation.

Contraindications, Warnings, Precautions and Adverse Events

QT Prolongation - Methadone should be used with caution in patients at risk for prolonged QT interval, especially in patients receiving medications known to prolong QT interval. QT prolongation has also been reported with high dose methadone in patients with no prior cardiac history.

Respiratory depression - Narcotics may produce serious or potentially fatal respiratory depression, especially when using excessive doses, at excessive frequencies, and in patients with compromised renal or hepatic function. Safe use of opioids requires dose individualization based on patients and pain characteristics. Use caution when giving opioid analgesics to patients receiving other agents that might cause respiratory depression. This includes many psychotropic medications in the drug classes of antidepressants, anxiolytics and sedative-hypnotics, as well as other respiratory depressants including alcohol. Respiratory depression secondary to chest wall rigidity has been reported with intravenous fentanyl administration, especially in the postoperative period. Respiratory depression can be reversed with opioid antagonists such as naloxone.

Seizures - Patients with known seizure disorders should be monitored closely if receiving meperidine, morphine, or hydromorphone. Post marketing reports of seizures have been associated with the use of tramadol, especially when used above recommended daily doses and with concurrent use of SSRIs, TCAs, neuroleptics or MAOIs.

Suicide - Do not use propoxyphene in patients who are suicidal or addiction prone. Accidental ingestion of excessive quantities of propoxyphene alone or in combinations with other medications such as acetaminophen has been reported. Do not exceed doses recommended by manufacturer.

Warnings, Precautions and Adverse Reactions Specific to Medications for Alcohol Dependence

Naltrexone - Should not be used in patients receiving opioid analgesics. Adverse events include abdominal pain, constipation, nausea and vomiting. Anxiety, nervousness, difficulty sleeping, fatigue, confusion, and irritability also reported.

Acamprosate - Attempted and completed suicides reported. Monitor for depression and/or suicidal thinking.

Disulfiram - Severe and sometimes fatal hepatitis and/or hepatic failure reported with or without prior history of abnormal hepatic function.



Opioid Medications Used for the Management of Pain

NAME	Codeine
SELECT BRAND NAMES	Tylenol with Codeine
PHARMACOKINETICS	A CYP 2D6 and 3A4 substrate and CYP 2D6 inhibitor that is well absorbed orally, with oral peak levels occurring within 1 to 2 hours; onset of analgesia is 30 to 60 minutes; duration of analgesic effect is 4 to 6 hours; elimination half-life is 2.5 to 3.5 hours; hepatic metabolism to an active metabolite (morphine) occurs and 3% to 16% excreted in the urine as unchanged compound, norcodeine, and free and conjugated morphine.
NRTIs	No evidence found for interactions with this class of medications
NNRTIs	No evidence found for interactions with this class of medications
Protease Inhibitors	
lopinavir/ritonavir (Kaletra)	Co-administration may increase serum levels of codeine. Use low doses and monitor closely.
ritonavir (Norvir)	Co-administration may increase serum levels of codeine. Use low doses and monitor closely.
Other Protease Inhibitors	No specific evidence found for interactions with atazanavir, darunavir, fosamprenavir, nelfinavir, indinavir, saquinavir, tipranavir. See ritonavir if using ritonavir boosted protease inhibitors.
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications
NAME	Fentanyl
SELECT BRAND NAMES	Actiq, Duragesic, Fentora, Sublimaze
PHARMACOKINETICS	A CYP 3A4 substrate that produces analgesia almost immediately following IV, lozenge/sucker, and oral transmucosal use; metabolism occurs in the liver and is excreted in the urine primarily as metabolites (less than 7% unchanged drug); the half life of fentanyl is 2 to 7 hours.
NRTIs	No evidence found for interactions with this class of medications
NNRTIs	
delavirdine (Rescriptor)	Co-administration may increase fentanyl levels
efavirenz (Sustiva)	Co-administration may decrease fentanyl levels
nevirapine (Viramune)	Co-administration may decrease fentanyl levels
etravirine (Intelligence)	Co-administration may decrease fentanyl levels
Protease Inhibitors	Combined administration of fentanyl and a protease inhibitor may increase fentanyl plasma concentrations, prolong fentanyl half-life, and increase potential for adverse drug reactions. Fentanyl is metabolized by cytochrome P450 3A4 isoenzymes (CYP3A4). Protease inhibitors are metabolized by and are inhibitors of CYP3A4.
lopinavir/ritonavir (Kaletra)	See ritonavir. Use with caution, monitor for excess sedation.
ritonavir (Norvir)	Co-administration with ritonavir may reduce clearance of fentanyl by 67% by inhibiting its metabolism. Potential for increase in fentanyl levels. Use with caution, monitor for excess sedation.



Opioid Medications Used for the Management of Pain

NAME	Fentanyl , cont'd
Other Protease Inhibitors	Co administration with atazanavir, darunavir, fosamprenavir, nelfinavir, indinavir, saquinavir, or tipranavir may lead to increased plasma fentanyl concentrations. See ritonavir if using ritonavir boosted protease inhibitors.
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications.
NAME	Hydrocodone
SELECT BRAND NAMES	Lortab, Norco, Vicodin
PHARMACOKINETICS	Peak analgesia generally occurs 2 hours following an oral dose; drug is well-absorbed from the gastrointestinal tract, producing peak serum levels in 1 hour; metabolism occurs in the liver to active metabolites; unchanged drug (12%) and metabolites excreted in the urine; half-life is approximately 4 hours.
NRTIs	No evidence found for interactions with this class of medications
NNRTIs	No evidence found for interactions with this class of medications
Protease Inhibitors	
lopinavir/ritonavir (Kaletra)	Co-administration may increase serum levels of hydrocodone. Use low doses and monitor closely.
ritonavir (Norvir)	Co-administration may increase serum levels of hydrocodone. Use low doses and monitor closely.
Other Protease Inhibitors	No specific evidence found for interactions with atazanavir, darunavir, fosamprenavir, nelfinavir, indinavir, saquinavir, or tipranavir. See ritonavir if using ritonavir boosted protease inhibitors.
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications
NAME	Hydromorphone
BRAND NAME	Dilaudid
PHARMACOKINETICS	Oral bioavailability is only 62% of the intravenous dose. Metabolism primarily occurs in the liver; majority of metabolites and unchanged drug excreted in the urine; parent compound has an elimination half-life of 2.5 hours.
NRTIs	No evidence found for interactions with this class of medications
NNRTIs	No evidence found for interactions with this class of medications
Protease Inhibitors	No evidence found for interactions with this class of medications
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications



Opioid Medications Used for the Management of Pain

NAME	Meperidine
BRAND NAME	Demerol
PHARMACOKINETICS	A CYP 2D6 substrate with an analgesic effect seen in 2 to 5 minutes when given intravenously or epidurally, in about 10 minutes after intramuscular (IM) or subcutaneous administration, and 20 to 30 minutes after oral (PO) dosing. Peak effect is seen 30 to 50 minutes after IM and 45 to 60 minutes after PO. Duration of analgesia is from 2 to 4 hours. When given orally, significant first-pass metabolism occurs, and less than 50% of the dose reaches systemic circulation. Metabolism primarily occurs in the liver to less active or inactive metabolites and excretes renally; half-life is approximately 3.5 hours; drug metabolizes to normeperidine (active metabolite), a CNS stimulant with a potential to accumulate in patients with renal disease (half-life is 15-50 hours).
NRTIs	No evidence found for interactions with this class of medications
NNRTIs	
delavirdine (Rescriptor)	Potential increase in meperidine levels when this combination is used.
Other NNRTIs	No evidence found for interactions with efavirenz, etravirine, or nevirapine
Protease Inhibitors	
lopinavir/ritonavir (Kaletra)	Data from studies with ritonavir suggest a decrease in meperidine effectiveness, though nor-meperidine levels increased. See ritonavir for additional details. Consider alternative narcotic analgesics.
ritonavir (Norvir)	Likely induction of metabolism - decrease in meperidine AUC by 62-67%, potentially decreasing meperidine effectiveness. Ritonavir may induce the metabolism of meperidine to its pharmacologically active metabolite, normeperidine. In one study, ritonavir (500 mg twice a day for 10 days) decreased the mean peak plasma concentration (Cmax) and area under the concentration-time curve (AUC) of meperidine (50 mg single oral dose) by 60% and 67%, respectively, compared to administration of meperidine alone. In contrast, normeperidine Cmax and AUC increased by 87% and 47%, suggesting induction of hepatic metabolism. Normeperidine has been associated with adverse effects such as lethargy, agitation, and seizures. Consider alternative narcotic analgesics.
Other Protease Inhibitors	No specific evidence found for interactions with atazanavir, darunavir, fosamprenavir, nelfinavir, indinavir, saquinavir, or tipranavir. See ritonavir if using ritonavir boosted protease inhibitors. Consider alternative narcotic analgesics.
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications



Opioid Medications Used for the Management of Pain

NAME	Morphine
SELECT BRAND NAMES	Avinza, Duramorph PF, Kadian, MS Contin, Oramorph SR, Roxanol, MSIR
PHARMACOKINETICS	Oral absorption is rapid, variable and has limited bioavailability; elimination half-life is 1.5 to 4.5 hours; hepatic metabolism via glucuronide conjugation to inactive metabolites is followed by renal excretion, 2% to 12% of unchanged drug, and fecal excretion of 7% to 10% of unchanged drug.
NRTIs	No evidence found for interactions with this class of medications
NNRTIs	No evidence found for interactions with this class of medications
Protease Inhibitors	No evidence found for interactions with this class of medications
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications
NAME	Oxycodone
SELECT BRAND NAMES	Oxycontin, Percocet, Percodan, Roxicet, Roxicodone, Oxyfast
PHARMACOKINETICS	A CYP 2D6 substrate with peak pain relief that occurs approximately 1 hour after administration and lasts for 3 to 4 hours; metabolism occurs in the liver. Peak pain relief for OxyContin(R) controlled-release tablets occurs approximately 1 hour after administration and lasts for 12 hours; steady-state plasma concentrations are achieved within 24 to 36 hours after initiation of therapy.
NRTIs	No evidence found for interactions with this class of medications
NNRTIs	No evidence found for interactions with this class of medications
Protease Inhibitors	Co-administration may increase serum levels of oxycodone. Use low doses and monitor closely.
lopinavir/ritonavir (Kaletra)	Co-administration may increase serum levels of oxycodone. Use low doses and monitor closely. Up to 3 fold increase in oxycodone when used with ritonavir.
ritonavir (Norvir)	
Other Protease Inhibitors	No evidence found for interactions with atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir. See ritonavir if using ritonavir boosted protease inhibitors.
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications



Opioid Medications Used for the Management of Pain

NAME	Pentazocine
SELECT BRAND NAMES	Talacen, Talwin
PHARMACOKINETICS	A CYP 2D6 substrate with oral absorption that is slow and incomplete; peak serum levels occur within 1 to 3 hours; onset of analgesia is within 15 to 30 minutes, with a peak effect at 1 to 3 hours and a duration of 4 to 5 hours; the peak analgesic effect occurs quicker with parenteral dosing (30 to 60 minutes); elimination half-life is 2 to 6 hours; extensive hepatic metabolism is followed by renal and fecal excretion of 5% to 8% and 1.5%, respectively, as unchanged drug.
NRTIs	No evidence found for interactions with this class of medications
NNRTIs	No evidence found for interactions with this class of medications
Protease Inhibitors	
lopinavir/ritonavir (Kaletra)	Co-administration with ritonavir may significantly increase pentazocine blood levels due to inhibition of CYP2D6.
ritonavir (Norvir)	Co-administration with ritonavir may significantly increase pentazocine blood levels due to inhibition of CYP2D6.
Other Protease Inhibitors	No evidence found for interactions with atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir. See ritonavir if using ritonavir boosted protease inhibitors.
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications
NAME	Propoxyphene
SELECT BRAND NAMES	Darvocet, Darvon
PHARMACOKINETICS	A CYP 3A4 inhibitor with peak serum concentrations with oral dosing occurring within 2 to 2.5 hours; pain relief lasts for 4 to 6 hours; elimination half-life is 6 to 12 h; extensive hepatic metabolism to both active and inactive metabolites is followed by renal excretion.
NRTIs	No evidence found for interactions with this class of medications
NNRTIs	
delavirdine (Rescriptor)	Propoxyphene and delavirdine are inhibitors of CYP3A4. Concurrent use may cause a potential increase in levels of propoxyphene
Other NNRTIs	No evidence found for interactions with efavirenz, etravirine, and nevirapine
Protease Inhibitors	Protease inhibitors, especially ritonavir, inhibit CYP3A4, potentially increasing levels of propoxyphene. Combination should be used with caution.
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications



Opioid Medications Used for the Management of Pain

NAME	Tramadol
BRAND NAME	Ultracet, Ultram
PHARMACOKINETICS	A CYP 2D6 substrate that is rapidly absorbed, with peak serum levels occurring within 2 hours; bioavailability is approximately 75% after a single oral dose but approaches 100% with regular scheduled doses extending over a week; metabolism occurs in the liver to an active metabolite (O-desmethyl tramadol); elimination half-life is approximately 6 to 7 hours.
NRTIs	No evidence found for interactions with this class of medications
NNRTIs	No evidence found for interactions with this class of medications
Protease Inhibitors	
lopinavir/ritonavir (Kaletra)	See ritonavir
ritonavir (Norvir)	Co-administration with ritonavir may increase the plasma concentrations of drugs that are substrates of the CYP450 2D6 isoenzyme. Caution is advised if ritonavir must be used concurrently with medications that undergo metabolism by CYP450 2D6. Consider avoiding or dosage reduction. Ritonavir inhibits CYP2D6 and may increase side effects of tramadol.
Other Protease Inhibitors	No evidence found for interactions with atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir. See ritonavir if using ritonavir boosted protease inhibitors.
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications

Opioid Medications Used for the Treatment of Opioid Dependence

NAME	Buprenorphine or Buprenorphine/Naloxone Combination Tablet
BRAND NAME	Buprenex, Subutex, Suboxone
PHARMACOKINETICS	Buprenorphine is 31% bioavailable when administered sublingually. Metabolism occurs in the liver; half-life of approximately 3 hours.
NRTIs	No evidence found for interactions with this class of medications.
NNRTIs	
delavirdine (Rescriptor)	Delavirdine significantly increases buprenorphine levels, though clinically relevant changes were not noted – Changes in dosage for either drug are not likely, though close monitoring is recommended.
efavirenz (Sustiva)	QT prolongation reported with delavirdine and buprenorphine administration, though not thought to be of clinical significance. Efavirenz significantly reduces buprenorphine levels, though clinically relevant withdrawal symptoms were not noted. Changes in dosage for either drug are not likely, though close monitoring is recommended.
etravirine (Intence)	This combination is currently under study. No data available when this update was published.
nevirapine (Viramune)	See clinicaltrials.gov for additional information No specific data with this combination. Based upon data with efavirenz, nevirapine is likely to reduce buprenorphine levels. Changes in doses may not be needed, though close monitoring is recommended.
Protease Inhibitors	
atazanavir (Reyataz)	Buprenorphine levels are increased by atazanavir and atazanavir/ritonavir, though atazanavir levels remained unchanged. Three patients reported increased sedation while receiving atazanavir/ritonavir with buprenorphine. Atazanavir or atazanavir/ritonavir is likely to increase buprenorphine levels, possibly requiring a dosage reduction in buprenorphine.
darunavir (Prezista)	When darunavir/ritonavir 600/100mg bid was added to buprenorphine/naloxone maintenance therapy, buprenorphine exposure was comparable with that following buprenorphine/naloxone alone. Buprenorphine metabolite (NorBUP) exposure was increased by 46%. The combination was generally well tolerated. Based on these findings, no adjustment of buprenorphine dosage is likely during darunavir/ritonavir. Close monitoring is recommended.
fosamprenavir (Lexiva)	The combination of buprenorphine and fosamprenavir is currently under study. No data available when this update was published. See ritonavir if using ritonavir boosted protease inhibitors. See clinicaltrials.gov for additional information.
indinavir (Crixivan)	No evidence found for this interaction. See ritonavir if using ritonavir boosted protease inhibitors.
lopinavir/ritonavir (Kaletra)	Buprenorphine levels were unchanged when used with lopinavir/ritonavir. Changes in dosages are not likely, though close monitoring is recommended.
nelfinavir (Viracept)	Buprenorphine levels were unchanged when used with nelfinavir. Changes in dosages are not likely, though close monitoring is recommended.
ritonavir (Norvir)	Buprenorphine levels are likely to be increased with concurrent use of ritonavir. Use caution when this is combination

Opioid Medications Used for the Treatment of Opioid Dependence

NAME	Buprenorphine or Buprenorphine/Naloxone Combination Tablet, cont'd
	is used. Close monitoring is recommended.
saquinavir (Invirase)	No evidence found for this interaction. See ritonavir if using ritonavir boosted protease inhibitors.
tipranavir (Aptivus)	Buprenorphine concentrations were unchanged when used concurrently with tipranavir/ritonavir, though tipranavir concentrations were reduced by about 20% and ritonavir concentrations decreased by 35%. Use caution when using this combination.
Integrase Inhibitors	The combination of buprenorphine and raltegravir is currently under study. No data available when this update was published. See clinicaltrials.gov for additional information
Entry Inhibitors	No evidence found for interactions with this class of medications
NAME	Methadone
BRAND NAME	Dolophine HCL
PHARMACOKINETICS	Metabolism occurs in the liver by CYP450 1A2, 2D6, and 3A4 system; racemic mixture of two enantiomers that is rapidly absorbed; onset of analgesia is 15 minutes when administered intravenously and 2 hours when taken orally; steady-state elimination half-life of 25 hours.
NRTIs	
abacavir (Ziagen)	Methadone causes a slight delay in the rate but not the extent of absorption of abacavir, leading to a 34% reduction in ABC exposure, but not altering antiviral activity.
stavudine (Zerit)	Methadone decreases stavudine levels by 25%
zidovudine (Retrovir)	Acute methadone treatment increased oral zidovudine AUC by 41-43% and reduced clearance by 21%, while chronic methadone treatment increased oral zidovudine AUC by 29% and reduced clearance by 26%.
Other NRTIs	No evidence found for interactions with didanosine enteric coated, emtricitabine, lamivudine or tenofovir.
NNRTIs	
delavirdine (Rescriptor)	Co-administration with delavirdine increases methadone levels; no observed toxicity.
efavirenz (Sustiva)	Due to CYP450 3A4 induction, efavirenz decreases methadone AUC by 52% and can result in severe withdrawal, potentially requiring a methadone dose increase. Monitor for withdrawal symptoms recommended.
etravirine (Intencele)	r-methadone AUC increased 8%; No clinically significant interaction found. Etravirine and methadone can be used concurrently without dosage adjustment, though monitoring for withdrawal symptoms is recommended.
nevirapine (Viramune)	Induction of methadone metabolism through CYP450 3A4 system leading to decreased plasma concentrations of methadone. Monitor for withdrawal symptoms recommended.

Opioid Medications Used for the Treatment of Opioid Dependence

NAME	Methadone, cont'd
Protease Inhibitors atazanavir (Reyataz) darunavir (Prezista)	Nevirapine 400mg once daily reduced methadone AUC by 63% in one study resulting in withdrawal symptoms and need for increased methadone dosage. Methadone has been shown to have no effect on atazanavir levels. Decreases methadone AUC 16%. Withdrawal symptoms unlikely with this reduction. Monitor for withdrawal symptoms recommended.
fosamprenavir (Lexiva)	Co-administration of amprenavir (or its prodrug, fosamprenavir) and methadone may result in a decrease in plasma concentrations of both drugs. The co-administration of abacavir plus amprenavir with methadone leads to a decrease in methadone levels. Use of fosamprenavir 700mg with ritonavir 100mg twice daily reduced r-methadone AUC by 18%. No patients experienced opioid withdrawal or intoxication.
indinavir (Crixivan)	Indinavir may potentially increase the plasma concentrations of methadone. One study found no change in methadone AUC and little or no change in indinavir AUC. Cmax of IDV was decreased while its Cmin was increased – unlikely clinically significant. Decreased methadone levels reported in vitro.
lopinavir/ritonavir (Kaletra)	Lopinavir/ritonavir can decrease methadone levels by 36 - 53%, but withdrawal symptoms unlikely. Use caution with this combination and monitor for withdrawal symptoms.
nelfinavir (Viracept)	Decreases methadone AUC by 47%, but no withdrawal symptoms observed. One study showed decreases in peak serum methadone levels of 37.8% and decreases in AUC of 36.3% when nelfinavir was co-administered. Case report of methadone withdrawal. Minimal effect on maintenance dose. May require an increase in methadone dose. In one study, co-administration may slightly decrease nelfinavir levels, while in another study, co-administration increases nelfinavir levels and decreases production of M8 metabolite.
saquinavir (Invirase)	20% reduction in methadone levels, when co-administered with saquinavir/ritonavir 400/400 mg BID. In one study, there was a 40% decrease in total S-methadone levels and 32% decrease in R-methadone AUC. In another study, there was no clinically significant interaction with co-administration of methadone with once-daily saquinavir/ritonavir 1600 mg/100 mg. Saquinavir 1000/100mg twice daily reduced methadone concentrations 19%.
Tipranavir (Aptivus)	R-methadone concentrations reduced by 49% when given concurrently with tipranavir/ritonavir. Monitor for opioid withdrawal symptoms.
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications



Opioid Medications Used for the Treatment of Opioid Dependence

NAME	Naloxone
BRAND NAME	Narcan, Suboxone, Talwin NX
PHARMACOKINETICS	Onset of effect is 2 to 3 minutes and duration is 45 minutes to 4 hours; elimination half-life is 30 to 100 minutes; rapid hepatic metabolism by conjugation with glucuronic acid is followed by 65% of an intravenous dose excreted renally as conjugated metabolites within 48 to 72 hours.
NRTIs	
abacavir (Ziagen)	Co-administration with abacavir may increase naloxone blood levels.
Other NRTIs	No evidence found for interactions with didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zidovudine
NNRTIs	No evidence found for interactions with this class of medications
Protease Inhibitors	
lopinavir/ritonavir (Kaletra)	See ritonavir
ritonavir (Norvir)	Co-administration may decrease plasma concentrations and AUC of naloxone.
Other Protease Inhibitors	No evidence found for interactions with atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir or tipranavir. See ritonavir if using ritonavir boosted protease inhibitors.
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications

Medications Used for the Treatment of Alcohol Dependence

NAME	Naltrexone
BRAND NAME	ReVia, Depade, Trexan
PHARMACOKINETICS	Almost complete absorption occurs, with peak plasma concentrations achieved 1 hour after oral administration; drug undergoes extensive first-pass hepatic metabolism; majority of unchanged drug and metabolites excretes in the urine; parent compound has a half-life of approximately 4 hours.
NRTIs	
zidovudine (Retrovir)	While there is evidence that no statistically significant differences in ZDV AUC were observed, in one study, co-administration increased the activity of zidovudine from 30 to 85%.
Other NRTIs	No evidence found for interactions with abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir
NNRTIs	No evidence found for interactions with this class of medications
Protease Inhibitors	
indinavir (Crixivan)	Co-administration with indinavir may increase antiviral activity of indinavir by 2-3 fold.
lopinavir/ritonavir (Kaletra)	See ritonavir
ritonavir (Norvir)	Co-administration with ritonavir may decrease plasma naltrexone concentrations and AUC.
Other Protease Inhibitors	No evidence found for interactions with atazanavir, darunavir, fosamprenavir, nelfinavir, saquinavir, tipranavir
Entry Inhibitors	No evidence found for interactions with this class of medications
Integrase Inhibitors	No evidence found for interactions with this class of medications
NAME	Acamprosate
BRAND NAME	Campral
PHARMACOKINETICS	Not metabolized; excreted in urine.
NRTIs	No evidence found for interactions with this class of medications
NNRTIs	No evidence found for interactions with this class of medications
Protease Inhibitors	No evidence found for interactions with this class of medications
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications



Medications Used for the Treatment of Alcohol Dependence

NAME	Disulfiram
BRAND NAME	Anatabuse
PHARMACOKINETICS	Metabolized in liver by various CYP450 enzymes, though classified as a weak inhibitor and/or substrate of most enzymes
NRTIs	No evidence found for interactions with this class of medications
NNRTIs	No evidence found for interactions with this class of medications
Protease Inhibitors	
lopinavir/ritonavir (Kaletra)	Lopinavir/ritonavir liquid contains large amounts of alcohol. Combination should be avoided
ritonavir (Norvir)	Ritonavir liquid contains alcohol. Combination should be avoided
tipranavir (Aptivus)	Tipranavir capsules contain alcohol. Combination should be avoided
Other Protease Inhibitors	No evidence found for interactions with atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir.
	See ritonavir
Integrase Inhibitors	No evidence found for interactions with this class of medications
Entry Inhibitors	No evidence found for interactions with this class of medications

RESOURCES

The National AETC Program also includes the following services:

National HIV/AIDS Clinicians Consultation Center: 1-800-933-3413

Offering treating clinicians current HIV clinical and drug information and individualized, expert case consultation.

Post-Exposure Prophylaxis 24 hour hotline: 1-888-HIV-4911

Providing consultation for occupational exposures.

Perinatal Hotline: 1-888-448-8765

Providing consultation for perinatal exposure and treatment.

AETC HIV/AIDS National Resource Center: <http://www.aidsetc.org/>

Providing resources (including curricula and lecture slide sets) on HIV disease treatment, education and data.

The following websites may be helpful in managing HIV infected patients:

AETC HIV/AIDS National Resource Center

www.aidsetc.org

NY/NJ AIDS Education and Training Center

www.nynjaetc.org

U.S. DHHS AIDS Info and Treatment Guidelines

www.aidsinfo.nih.gov

NYSDOH AIDS Institute Clinical Resources

www.hivguidelines.org

Substance Abuse and Mental Health Services Administration

www.samhsa.gov

Addiction Technology Transfer Center

www.natfc.org

Harm Reduction Coalition

www.harmreduction.org

RESOURCES

Data supporting this guide gathered from various sources including:

Micromedex® Health Care Series

Lexicomp® Online

Department of Health and Human Services Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents, December 1, 2009.

Facts and Comparisons 4.0® Available at www.aidsinfo.nih.gov

Food and Drug Administration Approved Product Labels

Various HIV related conference abstracts, posters and oral presentations

For Information on Substance Abuse and Opioid Addiction:

More information for treating professionals and for the public about medication assisted treatments for opioid addiction is available on-line and in print from the Substance Abuse and Mental Health Services Administration, part of the U.S. Department of Health and Human Services. To access, either link to www.samhsa.gov or www.buprenorphine.samhsa.gov.

For detailed references, training requests, or to order additional guides, please contact the NY/NJ AETC Central Office: (212) 304-5530.